

detect only *L pneumophila* serotype 1. Testing sputum samples using polymerase chain reaction has emerged as a highly sensitive method for diagnosing *Legionella*, and availability of this testing has become widespread.

► Treatment

Azithromycin (500 mg orally once daily), clarithromycin (500 mg orally twice daily), or a fluoroquinolone (eg, levofloxacin, 750 mg orally once daily), and not erythromycin, are the drugs of choice for treatment of legionellosis. Duration of therapy is 10–14 days, although a 21-day course of therapy is recommended for immunocompromised patients.

Cunha BA et al. Legionnaire's disease: a clinical diagnostic approach. Infect Dis Clin North Am. 2017;31:81. [PMID: 28159178]

Herwaldt LA et al. Legionella: a reemerging pathogen. Curr Opin Infect Dis. 2018;31:325. [PMID: 29794542]

GRAM-NEGATIVE BACTEREMIA & SEPSIS

Gram-negative bacteremia can originate in a number of sites, the most common being the genitourinary system, hepatobiliary tract, gastrointestinal tract, and lungs. Less common sources include intravenous lines, infusion fluids, surgical wounds, drains, and pressure injuries.

Patients with potentially fatal underlying conditions in the short term such as neutropenia or immunoparesis have a mortality rate of 40–60%; those with serious underlying diseases likely to be fatal in 5 years, such as solid tumors, cirrhosis, and aplastic anemia, die in 15–20% of cases; and individuals with no underlying diseases have a mortality rate of 5% or less.

► Clinical Findings

A. Symptoms and Signs

Most patients have fevers and chills, often with abrupt onset. However, 15% of patients are hypothermic (temperature 36.4°C or less) at presentation, and 5% never develop a temperature above 37.5°C. Hyperventilation with respiratory alkalosis and changes in mental status are important early manifestations. Hypotension and shock, which occur in 20–50% of patients, are unfavorable prognostic signs.

B. Laboratory Findings

Neutropenia or neutrophilia, often with increased numbers of immature forms of polymorphonuclear leukocytes, is the most common laboratory abnormality in septic patients. Thrombocytopenia occurs in 50% of patients, laboratory evidence of coagulation abnormalities in 10%, and overt disseminated intravascular coagulation in 2–3%. Both clinical manifestations and the laboratory abnormalities are nonspecific and insensitive, which accounts for the relatively low rate of blood culture positivity (approximately 20–40%). If possible, three blood cultures from separate sites should be obtained in rapid succession before starting antimicrobial therapy. The chance of recovering the organism in at least one of the three blood cultures is

greater than 95%. The false-negative rate for a single culture of 5–10 mL of blood is 30%. This may be reduced to 5–10% (albeit with a slight false-positive rate due to isolation of contaminants) if a single volume of 30 mL is inoculated into several blood culture bottles. Blood cultures may be falsely negative; when a patient with presumed septic shock, negative blood cultures, and inadequate explanation for the clinical course responds to antimicrobial agents, therapy should be continued for 10–14 days.

► Treatment

Several factors are important in the management of patients with sepsis.

A. Removal of Predisposing Factors

This usually means decreasing or stopping immunosuppressive medications and, in certain circumstances, giving granulocyte colony-stimulating factor (filgrastim; G-CSF) to the neutropenic patient.

B. Identifying the Source of Bacteremia

By simply finding the source of bacteremia and removing it (central venous catheter) or draining it (abscess), a fatal disease becomes easily treatable.

C. Supportive Measures

The use of fluids, vasopressors, and corticosteroids in septic shock is discussed in Chapter 14. Management of disseminated intravascular coagulation is discussed in Chapter 13.

D. Antibiotics

Antibiotics should be given as soon as the diagnosis is suspected, since delays in therapy have been associated with increased mortality rates, particularly once hypotension develops. In general, bactericidal antibiotics should be used and given intravenously to ensure therapeutic serum levels. Penetration of antibiotics into the site of primary infection is critical for successful therapy—ie, if the infection originates in the CNS, antibiotics that penetrate the blood-brain barrier should be used—eg, third- or fourth-generation cephalosporin—but not first-generation cephalosporins or aminoglycosides, which penetrate poorly. Sepsis caused by gram-positive organisms cannot be differentiated on clinical grounds from that due to gram-negative bacteria. Therefore, initial therapy should include antibiotics active against both types of organisms.

The number of antibiotics necessary remains controversial and depends on the cause. Table 30–4 provides a guide for empiric therapy. Although a combination of antibiotics is often recommended for “synergism,” combination therapy has not been shown to be superior to a single-drug regimen with any of several broad-spectrum antibiotics (eg, a third-generation cephalosporin, piperacillin-tazobactam, carbapenem). If multiple drugs are used initially, the regimen should be modified and coverage narrowed based on the results of culture and sensitivity testing.

Directed therapy for gram-negative bacteremia may be treated with as few as 7 days of antibiotic therapy.

Aillet C et al. Bacteraemia in emergency departments: effective antibiotic reassessment is associated with a better outcome. Eur J Clin Microbiol Infect Dis. 2018;37:325. [PMID: 29164361]

Rhodes A et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304. [PMID: 28101605]

Yahav D et al; Bacteremia Duration Study Group. Seven versus 14 days of antibiotic therapy for uncomplicated gram-negative bacteremia: a noninferiority randomized controlled trial. Clin Infect Dis. 2019;69:1091. [PMID: 30535100]

SALMONELLOSIS

Salmonellosis includes infection by any of approximately 2000 serotypes of salmonellae. All *Salmonella* serotypes are members of a single species, *Salmonella enterica*. Human infections are caused almost exclusively by *S enterica* subsp *enterica*, of which three serotypes—*typhi*, *typhimurium*, and *enteriditidis*—are predominantly isolated. Three clinical patterns of infection are recognized: (1) enteric fever, the best example of which is typhoid fever, due to serotype *typhi*; (2) acute enterocolitis, caused by serotype *typhimurium*, among others; and (3) the “septicemic” type, characterized by bacteremia and focal lesions, exemplified by infection with serotype *enteriditidis*. All types are transmitted by ingestion of the organism, usually from tainted food or drink.

1. Enteric Fever (Typhoid Fever)



ESSENTIALS OF DIAGNOSIS

- ▶ Gradual onset of headache, vomiting, abdominal pain.
- ▶ Rose spots, relative bradycardia, splenomegaly, and abdominal distention and tenderness.
- ▶ Slow (stepladder) rise of fever to maximum and then slow return to normal.
- ▶ Leukopenia; blood, stool, and urine cultures positive for *Salmonella*.

► General Considerations

Enteric fever is a clinical syndrome characterized by gastrointestinal symptoms as well as constitutional symptoms such as fever, malaise, and headache. It may have a long incubation period (6–30 days), and the gastrointestinal symptoms may resolve but then recur. Progressive infection often evolves with delirium. Enteric fever is caused by typhoidal strains of *Salmonella*, *S typhi* (typhoid fever) and to a lesser extent *S paratyphi* (subtypes A, B and C). Infection begins when organisms breach the mucosal epithelium of the intestines. Having crossed the epithelial barrier,

organisms invade and replicate in macrophages in Peyer patches, mesenteric lymph nodes, and the spleen. Serotypes other than *typhi* usually do not cause invasive disease, presumably because they lack the necessary human-specific virulence factors. Bacteremia occurs, and the infection then localizes principally in the lymphoid tissue of the small intestine. Peyer patches become inflamed and may ulcerate, with involvement greatest during the third week of disease. The organism may disseminate to the lungs, gallbladder, kidneys, or CNS.

► Clinical Findings

A. Symptoms and Signs

During the prodromal stage, there is increasing malaise, headache, cough, and sore throat, often with abdominal pain and constipation, while the fever ascends in a stepwise fashion. After about 7–10 days, it reaches a plateau and the patient is much more ill. There may be marked constipation, especially early, or “pea soup” diarrhea; marked abdominal distention occurs as well. If there are no complications, the patient’s condition will gradually improve over 7–10 days. However, relapse may occur for up to 2 weeks after defervescence.

During the early prodrome, physical findings are few. Later, splenomegaly, abdominal distention and tenderness, relative bradycardia, and occasionally meningismus appear. The rash (rose spots) commonly appears during the second week of disease. The individual spot, found principally on the trunk, is a pink papule 2–3 mm in diameter that fades on pressure. It disappears in 3–4 days.

B. Laboratory Findings

Unlike with other causes of gram-negative bacteremia, most patients with enteric fever do not have leukocytosis and leukopenia can be observed. Transaminitis is common. Typhoid fever is best diagnosed by blood culture, which is positive in the first week of illness in 80% of patients who have not taken antimicrobials. The rate of positivity declines thereafter, but one-fourth or more of patients still have positive blood cultures in the third week. Cultures of bone marrow occasionally are positive when blood cultures are not. Stool cultures are often negative by the time systemic symptoms develop.

► Differential Diagnosis

Enteric fever must be distinguished from other gastrointestinal illnesses and from other infections that have few localizing findings. Examples include tuberculosis, infective endocarditis, brucellosis, lymphoma, and Q fever. Often there is a history of recent travel to endemic areas, and viral hepatitis, malaria, or amebiasis may be in the differential.

► Complications

Complications occur in about 30% of untreated cases and account for 75% of deaths. Intestinal hemorrhage,

manifested by a sudden drop in temperature and signs of shock followed by dark or fresh blood in the stool, or intestinal perforation, accompanied by abdominal pain and tenderness, is most likely to occur during the third week. Appearance of leukocytosis and tachycardia should suggest these complications. Urinary retention, pneumonia, thrombophlebitis, myocarditis, neurologic complications, cholecystitis, nephritis, osteomyelitis, and meningitis are less often observed.

► Prevention

Immunization is not always effective but should be considered for household contacts of a typhoid carrier, for travelers to endemic areas, and during epidemic outbreaks. A multiple-dose oral vaccine and a single-dose parenteral vaccine are available. Their efficacies are similar, but oral vaccine causes fewer side effects. Boosters, when indicated, should be given every 5 years and 2 years for oral and parenteral preparations, respectively.

Adequate waste disposal and protection of food and water supplies from contamination are important public health measures to prevent salmonellosis. Carriers cannot work as food handlers.

► Treatment

A. Specific Measures

Because of increasing antimicrobial resistance, fluoroquinolones—such as ciprofloxacin 750 mg orally twice daily or levofloxacin 500 mg orally once daily, 5–7 days for uncomplicated enteric fever and 10–14 days for severe infection—are the agents of choice for treatment of *Salmonella* infections. Ceftriaxone, 2 g intravenously for 7 days, is also effective. Although resistance to fluoroquinolones or cephalosporins occurs uncommonly, the prevalence is increasing, and extensively drug-resistant *S typhi* has emerged in South Asia in recent years. When an infection is caused by a multidrug-resistant strain, select an antibiotic to which the isolate is susceptible in vitro. There is global resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole.

B. Treatment of Carriers

Ciprofloxacin, 750 mg orally twice a day for 4 weeks, has proved to be highly effective in eradicating the carrier state. Cholecystectomy may be used if prolonged antimicrobial therapy fails. When the isolate is susceptible, treatment of carriage with ampicillin, trimethoprim-sulfamethoxazole, or chloramphenicol may be successful.

► Prognosis

The mortality rate of typhoid fever is about 2% in treated cases. Elderly or debilitated persons are likely to do worse. With complications, the prognosis is poor. Relapses occur in up to 15% of cases. A residual carrier state frequently persists in spite of therapy.

Gibani MM et al. Typhoid and paratyphoid fever: a call to action. *Curr Opin Infect Dis.* 2018;31:440. [PMID: 30138141]
Wain J et al. Typhoid fever. *Lancet.* 2015;385:1136. [PMID: 25458731]

2. *Salmonella* Gastroenteritis

By far the most common form of salmonellosis is acute enterocolitis, which can be caused by both typhoidal and non-typhoidal *Salmonella*. The incubation period is 8–48 hours after ingestion of contaminated food or liquid.

Symptoms and signs consist of fever (often with chills), nausea and vomiting, cramping abdominal pain, and diarrhea, which may be grossly bloody, lasting 3–5 days. Differentiation must be made from viral gastroenteritis, food poisoning, shigellosis, amebic dysentery, and acute ulcerative colitis. The diagnosis is made by culturing the organism from the stool. The disease is usually self-limited, but bacteremia with localization in joints or bones may occur, especially in patients with sickle cell disease.

In most cases, treatment of uncomplicated enterocolitis is symptomatic only as most illnesses are self-limited and antimicrobial treatment may prolong bacterial shedding. However, patients who are malnourished or severely ill, patients with sickle cell disease, and patients who are immunocompromised (including those who are HIV-positive) should be treated with ciprofloxacin, 500 mg orally twice a day; ceftriaxone, 1 g intravenously once daily; trimethoprim-sulfamethoxazole, 160 mg/80 mg orally twice a day; or azithromycin, 500 mg orally once daily for 7–14 days (14 days for immunocompromised patients).

Shane AL et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis.* 2017;65:1963. [PMID: 29194529]

3. *Salmonella* Bacteremia

Salmonella infection may be manifested by prolonged or recurrent fevers accompanied by bacteremia and local infection in bone, joints, pleura, pericardium, lungs, or other sites. Mycotic aortic aneurysms may also occur. This complication of bacteremia tends to occur in immunocompromised persons, including HIV-infected individuals, or in older adults with preexisting aneurysms or atherosclerotic plaques. Serotypes other than *typhi* usually are isolated. Treatment requires systemic antimicrobial therapy (duration depends on the site of infection) plus drainage of any abscesses. In HIV-infected patients, relapse is common, and lifelong suppressive therapy may be needed. Ciprofloxacin, 750 mg orally twice a day, is effective both for therapy of acute infection and for suppression of recurrence. Incidence of infections caused by drug-resistant strains may be on the rise.

Crump JA et al. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive *Salmonella* infections. *Clin Microbiol Rev.* 2015;28:901. [PMID: 26180063]

SHIGELLOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Diarrhea, often with blood and mucus.
- ▶ Crampy abdominal pain and systemic toxicity.
- ▶ Leukocytes in stool; positive stool culture.

► General Considerations

Shigella dysentery is a common disease, often self-limited and mild but occasionally serious. *S sonnei* is the leading cause in the United States, followed by *S flexneri*. *S dysenteriae* causes the most serious form of the illness. Shigellae are invasive organisms. The infective dose is low at 10^2 – 10^3 organisms. There has been a rise in strains resistant to multiple antibiotics.

► Clinical Findings

A. Symptoms and Signs

The illness usually starts abruptly, with diarrhea, lower abdominal cramps, and tenesmus. The diarrheal stool often is mixed with blood and mucus. Systemic symptoms are fever, chills, anorexia and malaise, and headache. The abdomen is tender. Sigmoidoscopic examination reveals an inflamed, engorged mucosa with punctate and sometimes large areas of ulceration.

B. Laboratory Findings

The stool shows many leukocytes and red cells. Stool culture is positive for *Shigella* in most cases, but blood cultures grow the organism in less than 5% of cases.

► Differential Diagnosis

Bacillary dysentery must be distinguished from salmonella enterocolitis and from disease due to enterotoxigenic *Escherichia coli*, *Campylobacter*, and *Yersinia enterocolitica*. Amebic dysentery may be similar clinically and is diagnosed by finding amoebas in the fresh stool specimen. Ulcerative colitis is another cause of bloody diarrhea.

► Complications

Temporary disaccharidase deficiency may follow the diarrhea. Reactive arthritis is an uncommon complication, usually occurring in HLA-B27 individuals infected by *Shigella*. Hemolytic-uremic syndrome occurs rarely.

► Treatment

Treatment of dehydration and hypotension is lifesaving in severe cases. Recommended empiric antimicrobial therapy is either a fluoroquinolone (ciprofloxacin, 750 mg orally twice daily for 7–10 days, or levofloxacin, 500 mg orally once daily for 3 days) or ceftriaxone, 1 g intravenously once daily for 5 days. If the isolate is susceptible, trimethoprim-sulfamethoxazole, 160/80 mg orally twice

daily for 5 days, or azithromycin, 500 mg orally once daily for 3 days, is also effective. High rates of resistance to amoxicillin make it a less effective treatment option.

Goulart MA et al. Shigellosis in men who have sex with men: an overlooked opportunity to counsel with pre-exposure prophylaxis for HIV. *Int J STD AIDS*. 2016;27:1236. [PMID: 26945593]

Shane AL et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65:1963. [PMID: 29194529]

GASTROENTERITIS CAUSED BY *ESCHERICHIA COLI*

E coli causes gastroenteritis by a variety of mechanisms. Enterotoxigenic *E coli* (ETEC) elaborates either a heat-stable or heat-labile toxin that mediates the disease. ETEC is an important cause of traveler's diarrhea. Enteroinvasive *E coli* (EIEC) differs from other *E coli* bowel pathogens in that these strains invade cells, causing bloody diarrhea and dysentery similar to infection with *Shigella* species. EIEC is uncommon in the United States. Neither ETEC nor EIEC strains are routinely isolated and identified from stool cultures because there is no selective medium. Antimicrobial therapy against *Salmonella* and *Shigella*, such as ciprofloxacin 500 mg orally twice daily, shortens the clinical course, but the disease is self-limited.

Shiga-toxin-producing *E coli* (STEC) infection can result in asymptomatic carrier stage, nonbloody diarrhea, hemorrhagic colitis, hemolytic-uremic syndrome, or thrombotic thrombocytopenic purpura. Although *E coli* O157:H7 is responsible for most cases of STEC infection in the United States, other STEC strains that cause severe disease (such as *E coli* O104:H4) have been reported in Europe. *E coli* O157:H7 has caused several outbreaks of diarrhea and hemolytic-uremic syndrome related to consumption of undercooked hamburger, raw flour, unpasteurized apple juice, and spinach, while *E coli* O145 was linked to the consumption of contaminated lettuce. Older individuals and young children are most affected, with hemolytic-uremic syndrome being more common in the latter group. STEC identification can be difficult. The CDC recommends that all stools submitted for routine testing from patients with acute community-acquired diarrhea be simultaneously cultured for *E coli* O157:H7 and tested for Shiga toxins to detect non-O157 STEC, such as *E coli* O145. Antimicrobial therapy does not alter the course of the disease and may increase the risk of hemolytic-uremic syndrome. Treatment is primarily supportive. Hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura occurring in association with a diarrheal illness suggests the diagnosis and should prompt evaluation for STEC. Confirmed infections should be reported to public health officials.

Tack D et al. Preliminary incidence and trends of infections with pathogens transmitted commonly through food—Foodborne Diseases Active Surveillance Network, 10 U.S. Sites, 2016–2019. *MMWR Morb Mortal Wkly Rep*. 2020;69:508. [PMID: 3235295]

CHOLERA



ESSENTIALS OF DIAGNOSIS

- ▶ History of travel in endemic area or contact with infected person.
- ▶ Voluminous diarrhea (up to 15 L/day).
- ▶ Characteristic “rice water stool.”
- ▶ Rapid development of marked dehydration.
- ▶ Positive stool cultures.

General Considerations

Cholera is an acute diarrheal illness caused by certain serotypes of *Vibrio cholerae*. The disease is toxin-mediated, and fever is unusual. The toxin activates adenylyl cyclase in intestinal epithelial cells of the small intestines, producing hypersecretion of water and chloride ion and a massive diarrhea of up to 15 L/day. Death results from profound hypovolemia. Cholera occurs in epidemics under conditions of crowding, war, and famine (eg, in refugee camps) and where sanitation is inadequate. Infection is acquired by ingestion of contaminated food or water. The most recent outbreak of cholera in the Western Hemisphere occurred in Haiti in late 2010, when there was a massive earthquake followed by a cholera outbreak that resulted in thousands of deaths.

Clinical Findings

Cholera is characterized by a sudden onset of severe, frequent watery diarrhea (up to 1 L/h). The liquid stool is gray; turbid; and without fecal odor, blood, or pus (“rice water stool”). Dehydration and hypotension develop rapidly. Stool cultures are positive, and agglutination of vibrios with specific sera can be demonstrated. Rapid antigen and PCR-based testing is also available.

Treatment

Treatment is primarily by replacement of fluids. In mild or moderate illness, oral rehydration usually is adequate. A simple oral replacement fluid can be made from 1/2 teaspoon of table salt and 6 level teaspoons of sugar added to 1 L of water. Intravenous fluids are indicated for persons with signs of severe hypovolemia and those who cannot take adequate fluids orally. Lactated Ringer infusion is satisfactory.

Antimicrobial therapy will shorten the course of illness and is indicated for severely ill patients. Antimicrobials active against *V cholerae* include tetracycline, ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, fluoroquinolones, and azithromycin. Multidrug-resistant strains exist, so susceptibility testing, if available, is advisable. A single 1 g oral dose of azithromycin is effective for severe cholera caused by strains with reduced susceptibility to fluoroquinolones, but resistance is emerging to this drug as well.

Prevention

Oral cholera vaccines are available that confer short-lived, limited protection and may be required for entry into or reentry after travel to some countries. One live attenuated oral vaccine is approved for use in the United States for persons traveling to areas of active cholera transmission, but supplies may be limited or unavailable.

Vaccination programs are expensive and not particularly effective in managing outbreaks of cholera. When outbreaks occur, efforts should be directed toward establishing clean water and food sources and proper waste disposal.

Clemens JD et al. Cholera. Lancet. 2017;390:1539. [PMID: 28302312]

Wong KK et al. Recommendations of the Advisory Committee on Immunization Practices for use of cholera vaccine. MMWR Morb Mortal Wkly Rep. 2017;66:482. [PMID: 28493859]

INFECTIONS CAUSED BY OTHER *VIBRIO* SPECIES

Vibrios other than *V cholerae* that cause human disease are *Vibrio parahaemolyticus*, *V vulnificus*, and *V alginolyticus*. All are halophilic marine organisms. Infection is acquired by exposure to organisms in contaminated, undercooked, or raw crustaceans or shellfish and warm (greater than 20°C [82.4°F]) ocean waters and estuaries. Infections are more common during the summer months from regions along the Atlantic coast and the Gulf of Mexico in the United States and from tropical waters around the world. Oysters are implicated in up to 90% of food-related cases. *V parahaemolyticus* causes an acute watery diarrhea with crampy abdominal pain and fever, typically occurring within 24 hours after ingestion of contaminated shellfish. The disease is self-limited, and antimicrobial therapy is usually not necessary. *V parahaemolyticus* may also cause cellulitis and sepsis, though these findings are more characteristic of *V vulnificus* infection.

V vulnificus and *V alginolyticus*—neither of which is associated with diarrheal illness—are important causes of cellulitis, wound infections, and primary bacteremia following exposure to sea water or ingestion of contaminated shellfish. Cellulitis with or without sepsis may be accompanied by bulla formation and necrosis with extensive soft tissue destruction, at times requiring debridement and amputation. The infection can be rapidly progressive and is particularly severe in immunocompromised individuals—especially those with cirrhosis—with death rates as high as 50%. Patients with chronic liver disease and those who are immunocompromised should be cautioned to avoid eating raw oysters.

Doxycycline 100 mg orally twice daily plus ceftazidime for 7–10 days is the drug of choice for treatment of suspected or documented primary bacteremia or cellulitis caused by *Vibrio* species. *V vulnificus* is susceptible in vitro to penicillin, ampicillin, cephalosporins, chloramphenicol, aminoglycosides, and fluoroquinolones, and these agents may also be effective. *V parahaemolyticus* and *V alginolyticus* produce beta-lactamase and therefore are resistant to penicillin and ampicillin, but susceptibilities otherwise are similar to those listed for *V vulnificus*.

Baker-Austin C et al. *Vibrio vulnificus*: new insights into a deadly opportunistic pathogen. *Environ Microbiol*. 2018;20:423. [PMID: 29027375]

Wong KC et al. Antibiotic use for *Vibrio* infections: important insights from surveillance data. *BMC Infect Dis*. 2015;15:226. [PMID: 26062903]

INFECTIONS CAUSED BY CAMPYLOBACTER SPECIES

Campylobacter organisms are microaerophilic, motile, gram-negative rods. Two species infect humans: *Campylobacter jejuni*, an important cause of diarrheal disease, and *C fetus* subsp *fetus*, which typically causes systemic infection and less frequently gastroenteritis. Dairy cattle and poultry are an important reservoir for campylobacters. Outbreaks of enteritis have been associated with consumption of raw milk. *Campylobacter* gastroenteritis is associated with fever, abdominal pain, and diarrhea characterized by loose, watery, or bloody stools. The differential diagnosis includes shigellosis, *Salmonella* gastroenteritis, and enteritis caused by *Y enterocolitica* or invasive *E coli*. The disease is self-limited, but its duration can be shortened with antimicrobial therapy. Either azithromycin, 1 g orally as a single dose, or ciprofloxacin, 500 mg orally twice daily for 3 days, is effective therapy. However, *C jejuni* isolates may be resistant to fluoroquinolone, particularly in Southeast Asia, and susceptibility testing should be routinely performed.

C fetus causes systemic infections that can be fatal, including primary bacteremia, endocarditis, meningitis, and focal abscesses. It infrequently causes gastroenteritis. Patients infected with *C fetus* are often older, debilitated, or immunocompromised. Closely related species, collectively termed “campylobacter-like organisms,” cause bacteremia in HIV-infected individuals. Systemic infections respond to therapy with gentamicin, carbapenems, ceftriaxone, or ciprofloxacin. Ceftriaxone, meropenem, or chloramphenicol should be used to treat infections of the CNS because of their ability to penetrate the blood-brain barrier.

Shane AL et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65:1963. [PMID: 29194529]

TULAREMIA



ESSENTIALS OF DIAGNOSIS

- ▶ History of contact with rabbits, other rodents, and biting ticks in summer in endemic area.
- ▶ Fever, headache, nausea, and prostration.
- ▶ Papule progressing to ulcer at site of inoculation.
- ▶ Enlarged regional lymph nodes.
- ▶ Positive serologic tests or culture of ulcer, lymph node aspirate, or blood.

► General Considerations

Tularemia is a zoonotic infection of wild rodents and rabbits caused by *Francisella tularensis*. Humans usually acquire the infection by contact with animal tissues (eg, trapping muskrats, skinning rabbits) or from a tick or insect bite. Hamsters and prairie dogs also may carry the organism. An outbreak of pneumonic tularemia in 2000 on Martha’s Vineyard in Massachusetts was linked to lawn-mowing and brush-cutting as risk factors for infection, underscoring the potential for probable aerosol transmission of the organism. *F tularensis* has been classified as a high-priority agent for potential bioterrorism use because of its virulence and relative ease of dissemination. Infection in humans often produces a local lesion and widespread organ involvement but may be entirely asymptomatic. The incubation period is typically 3–5 days.

► Clinical Findings

A. Symptoms and Signs

Fever, headache, and nausea begin suddenly, and a local lesion—a papule at the site of inoculation—develops and soon ulcerates. Regional lymph nodes may become enlarged and tender and may suppurate. The local lesion may be on the skin of an extremity or in the eye. Pneumonia may develop from hematogenous spread of the organism or may be primary after inhalation of infected aerosols. Following ingestion of infected meat or water, an enteric form may be manifested by gastrointestinal symptoms, stupor, and delirium. In any type of involvement, the spleen may be enlarged and tender and there may be non-specific rashes, myalgias, and prostration.

B. Laboratory Findings

Culturing the organism from blood or infected tissue requires special media. For this reason and because cultures of *F tularensis* may be hazardous to laboratory personnel, the diagnosis is usually made serologically. A positive agglutination test (greater than 1:80) develops in the second week after infection and may persist for several years.

► Differential Diagnosis

Tularemia must be differentiated from rickettsial and meningococcal infections, cat-scratch disease, infectious mononucleosis, and various bacterial and fungal diseases.

► Complications

Hematogenous spread may produce meningitis, periprosthetic joint炎, pericarditis, pneumonia, and osteomyelitis.

► Treatment

Streptomycin is the drug of choice; the recommended dose is 7.5 mg/kg intramuscularly every 12 hours for 7–14 days. Gentamicin, which has good in vitro activity against *F tularensis*, is generally less toxic than streptomycin but some case series report lower treatment success rates. Doxycycline (200 mg/day orally) is also effective but has a higher relapse rate and should only be used for the less

seriously ill. A variety of other agents (eg, fluoroquinolones) are active in vitro, but their clinical effectiveness is not well established.

Maurin M et al. Tularaemia: clinical aspects in Europe. *Lancet Infect Dis*. 2016;16:113. [PMID: 26738841]

PLAQUE



ESSENTIALS OF DIAGNOSIS

- ▶ History of exposure to rodents in endemic area.
- ▶ Sudden onset of high fever, muscular pains, and prostration.
- ▶ Axillary, cervical, or inguinal lymphadenitis (bubo).
- ▶ Pustule or ulcer at inoculation site.
- ▶ Pneumonia or meningitis is often fatal.
- ▶ Positive smear and culture from bubo and positive blood culture.

General Considerations

Plague is a zoonotic infection carried by wild rodents and caused by *Yersinia pestis*, a small bipolar-staining gram-negative rod. It is endemic in California, Arizona, Nevada, and New Mexico. Worldwide, Madagascar accounts for three-quarters of the global burden. It is transmitted among rodents and to humans by the bites of fleas or from contact with infected animals. Following a flea bite, the organisms spread through the lymphatics to the lymph nodes, which become greatly enlarged (bubo). They may then reach the bloodstream to involve all organs. When pneumonia or meningitis develops, the outcome is often fatal. The patient with pneumonia can transmit the infection to other individuals by droplets. The incubation period is 2–10 days. Because of its extreme virulence, its potential for dissemination and person-to-person transmission, and efforts to develop the organism as an agent of biowarfare, plague bacillus is considered a high-priority agent for bioterrorism.

Clinical Findings

A. Symptoms and Signs

The onset is sudden, with high fever, malaise, tachycardia, intense headache, delirium, and severe myalgias. The patient appears profoundly ill. If pneumonia develops, tachypnea, productive cough, blood-tinged sputum, and cyanosis also occur. There may be signs of meningitis. A pustule or ulcer at the site of inoculation may be observed. Axillary, inguinal, or cervical lymph nodes become enlarged and tender and may suppurate and drain. With hematogenous spread, the patient may rapidly become toxic and comatose, with purpuric spots (black plague) appearing on the skin.

Primary plague pneumonia is a fulminant pneumonitis with bloody, frothy sputum and sepsis. It is usually fatal unless treatment is started within a few hours after onset.

B. Laboratory Findings

The plague bacillus may be found in smears from aspirates of buboes examined with Gram stain. Cultures from bubo aspirate or pus and blood are positive but may grow slowly. In convalescing patients, an antibody titer rise may be demonstrated by agglutination tests.

Differential Diagnosis

The lymphadenitis of plague is most commonly mistaken for the lymphadenitis accompanying staphylococcal or streptococcal infections of an extremity, sexually transmitted diseases such as lymphogranuloma venereum or syphilis, and tularemia. The systemic manifestations resemble those of enteric or rickettsial fevers, malaria, or influenza. The pneumonia resembles other bacterial pneumonias, and the meningitis is similar to those caused by other bacteria.

Prevention

Avoiding exposure to rodents and fleas in endemic areas is the best prevention strategy. Drug prophylaxis may provide temporary protection for persons exposed to the risk of plague infection, particularly by the respiratory route. Doxycycline, 100 mg orally twice daily for 7 days, is effective. No vaccine is available at this time.

Treatment

Therapy should be started immediately once plague is suspected. Either streptomycin (the agent with which there is greatest experience), 1 g every 12 hours intravenously, or gentamicin, administered as a 2-mg/kg loading dose, then 1.7 mg/kg every 8 hours intravenously, is effective. Alternatively, doxycycline, 100 mg orally or intravenously, may be used. The duration of therapy is 10 days. Patients with plague pneumonia are placed in strict respiratory isolation, and prophylactic therapy is given to any person who came in contact with the patient.

Yang R. Plague: recognition, treatment, and prevention. *J Clin Microbiol*. 2018;56:e01519. [PMID: 29070654]

GONOCOCCAL INFECTIONS



ESSENTIALS OF DIAGNOSIS

- ▶ Purulent, profuse urethral discharge with dysuria, especially in men; yields positive smear.
- ▶ **Men:** urethritis, epididymitis, prostatitis, proctitis, pharyngitis.
- ▶ **Women:** cervicitis with purulent discharge, or asymptomatic, yielding positive culture; vaginitis, salpingitis, proctitis also occur.
- ▶ **Disseminated disease:** fever, rash, tenosynovitis, and arthritis.
- ▶ The preferred method of diagnosis is testing with nucleic acid amplification.

► General Considerations

Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus typically found inside polymorphonuclear cells. It is transmitted during sexual activity and has its greatest incidence in the 15- to 29-year-old age group. The incubation period is usually 2–8 days.

► Classification

A. Urethritis and Cervicitis

Initial symptoms seen in men include burning on urination and a serous or milky discharge. One to 3 days later, the urethral pain is more pronounced and the discharge becomes yellow, creamy, and profuse, sometimes blood-tinged. The disorder may regress and become chronic or progress to involve the prostate, epididymis, and periurethral glands with painful inflammation. Chronic infection leads to prostatitis and urethral strictures. Rectal infection is common in men who have sex with men. Other sites of primary infection (eg, the pharynx) must always be considered. Asymptomatic infection is common and occurs in both sexes.

Gonococcal infection in women often presents with dysuria, urinary frequency, and urgency, with a purulent urethral discharge. Vaginitis and cervicitis with inflammation of Bartholin glands are common. Infection may be asymptomatic, with only slightly increased vaginal discharge and moderate cervicitis on examination. Infection may remain as a chronic cervicitis—an important reservoir of gonococci. It can progress to involve the uterus and tubes with acute and chronic salpingitis, with scarring of tubes and sterility. In pelvic inflammatory disease, anaerobes and chlamydia often accompany gonococci. Rectal infection may result from spread of the organism from the genital tract or from anal coitus.

Nucleic acid amplification tests are the preferred method for diagnosing gonorrhea at all sites given their excellent sensitivity and specificity. In women with suspected cervical infection, endocervical or vaginal swabs (clinician- or self-collected) as well as first catch am urine specimen (later specimens have 10% reduced sensitivity) are options. In men with urethral infection, first catch am urine is recommended. Nucleic acid amplification tests are also recommended by the CDC for oropharyngeal and rectal site swab testing. Urine testing does not detect oropharyngeal and rectal gonorrhea unless there is concurrent genital infection. Gram stain of urethral or rectal discharge in men, especially during the first week after onset, shows gram-negative diplococci in polymorphonuclear leukocytes. Gram stain is less often positive in women. Cultures should still be obtained when evaluating a treatment failure to assess for antimicrobial resistance.

B. Disseminated Disease

Systemic complications follow the dissemination of gonococci from the primary site via the bloodstream. Two distinct clinical syndromes—either purulent arthritis or the triad of rash, tenosynovitis, and arthralgias—are commonly observed in patients with disseminated gonococcal infection, although overlap can be seen. The skin lesions

can range from maculopapular to pustular or hemorrhagic, which tend to be few in number and peripherally located. The tenosynovitis is often found in the hands and wrists and feet and ankles. These unique findings can help distinguish among other infectious syndromes. The arthritis can occur in one or more joints and may be migratory. Gonococci are isolated by culture from less than half of patients with gonococcal arthritis. Nucleic acid amplification can be performed on synovial fluid, if available, and may be more sensitive for the diagnosis. Rarely, gonococcal endocarditis or meningitis develops.

C. Conjunctivitis

The most common form of eye involvement is direct inoculation of gonococci into the conjunctival sac. In adults, this occurs by autoinoculation of a person with genital infection. The purulent conjunctivitis may rapidly progress to panophthalmitis and loss of the eye unless treated promptly.

► Differential Diagnosis

Gonococcal urethritis or cervicitis must be differentiated from nongonococcal urethritis; cervicitis or vaginitis due to *Chlamydia trachomatis*, *Gardnerella vaginalis*, *Trichomonas*, *Candida*, and other pathogens associated with sexually transmitted diseases; and pelvic inflammatory disease, arthritis, proctitis, and skin lesions. Often, several such pathogens coexist in a patient. Reactive arthritis (urethritis, conjunctivitis, arthritis) may mimic gonorrhea or coexist with it.

► Prevention

Prevention is based on education and mechanical or chemical prophylaxis. The condom, if properly used, can reduce the risk of infection. Partner notification and referral of contacts for treatment has been the standard method used to control sexually transmitted diseases. Early treatment of contacts can halt the development of symptoms as well. Expedited treatment of sex partners by patient-delivered partner therapy is more effective than partner notification in reducing persistence and recurrence rates of gonorrhea and chlamydia.

► Treatment

Therapy typically is administered before antimicrobial susceptibilities are known. The choice of which regimen to use should be based on the national prevalence of antibiotic-resistant organisms. Nationwide, there are strains of gonococci that are resistant to penicillin, tetracycline, or ciprofloxacin. Consequently, these drugs are not considered first-line therapy. Resistance to azithromycin and to ceftriaxone has been reported. All sexual partners should be treated and tested for HIV infection and syphilis, as should the patient.

A. Uncomplicated Gonorrhea

Due to increasing resistance of *N gonorrhoeae* to cephalosporins, the CDC recommends a high dose of intramuscular

ceftriaxone when chlamydial infection has been excluded. For uncomplicated gonococcal infections of the cervix, urethra, rectum, and pharynx, the recommended treatment is ceftriaxone (500 mg intramuscularly for patients who weigh less than 105 kg and 1 g intramuscularly for patients who weigh 150 kg or more). Cefixime, 800 mg orally as a single dose, should be used when an oral cephalosporin is the only option. When chlamydial infection has not been excluded, co-treatment of chlamydia with doxycycline 100 mg twice daily for 7 days or azithromycin 1 g as a single dose is recommended. Fluoroquinolones are not recommended for treatment due to high rates of microbial resistance. Spectinomycin, 1 g intramuscularly once, may be used for the penicillin-allergic patient but is not currently available in the United States.

B. Treatment of Other Infections

Disseminated gonococcal infection (including arthritis and arthritis-dermatitis syndromes) should be treated with ceftriaxone (1 g intravenously daily) plus azithromycin (1000 mg orally as a single dose), until 48 hours after improvement begins, at which time therapy may be switched to cefixime (400 mg orally daily) to complete at least 1 week of antimicrobial therapy. Endocarditis should be treated with ceftriaxone (2 g every 24 hours intravenously) for at least 4 weeks.

Pelvic inflammatory disease requires cefoxitin (2 g intravenously every 6 hours) or cefotetan (2 g intravenously every 12 hours) plus doxycycline (100 mg every 12 hours). Clindamycin (900 mg intravenously every 8 hours) plus gentamicin (administered intravenously as a 2-mg/kg loading dose followed by 1.5 mg/kg every 8 hours) is also effective. Ceftriaxone (250 mg intramuscularly as a single dose) or cefoxitin (2 g intramuscularly) plus probenecid (1 g orally as a single dose) plus doxycycline (100 mg twice a day for 14 days), with or without metronidazole (500 mg twice daily for 14 days), is an effective outpatient regimen.

De Ambrogi M. International forum on gonococcal infections and resistance. Lancet Infect Dis. 2017;17:1127. [PMID: 29115267]

St Cyr S et al. Update to CDC's treatment guidelines for gonococcal infection, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1911. [PMID: 33332296]

CHANCRID

Chancroid is a sexually transmitted disease caused by the short gram-negative bacillus *Haemophilus ducreyi*. The incubation period is 3–5 days. At the site of inoculation, a vesicopustule develops that breaks down to form a painful, soft ulcer with a necrotic base, surrounding erythema, and undermined edges. There may be multiple lesions due to autoinoculation. The adenitis is usually unilateral and consists of tender, matted nodes of moderate size with overlying erythema. These may become fluctuant and rupture spontaneously. With lymph node involvement, fever, chills, and malaise may develop. Balanitis and phimosis are frequent complications in men. Women may have no external signs of infection. The diagnosis is established by culturing a swab of the lesion onto a special medium.

Chancroid must be differentiated from other genital ulcers. The chancre of syphilis is clean and painless, with a hard base. Mixed sexually transmitted disease is very common (including syphilis, herpes simplex, and HIV infection), as is infection of the ulcer with fusiforms, spirochetes, and other organisms.

A single dose of either azithromycin, 1 g orally, or ceftriaxone, 250 mg intramuscularly, is effective treatment. Effective multiple-dose regimens are erythromycin, 500 mg orally four times a day for 7 days, or ciprofloxacin, 500 mg orally twice a day for 3 days.

Romero L et al. Macrolides for treatment of *Haemophilus ducreyi* infection in sexually active adults. Cochrane Database Syst Rev. 2017;12:CD012492. [PMID: 29226307]

GRANULOMA INGUINALE

Granuloma inguinale is a chronic, relapsing granulomatous anogenital infection due to *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*). The pathognomonic cell, found in tissue scrapings or secretions, is large (25–90 μm), and contains intracytoplasmic cysts filled with bodies (Donovan bodies) that stain deeply with Wright stain.

The incubation period is 8 days to 12 weeks. The onset is insidious. The lesions occur on the skin or mucous membranes of the genitalia or perineal area. They are relatively painless infiltrated nodules that soon slough. A shallow, sharply demarcated ulcer forms, with a beefy-red friable base of granulation tissue. The lesion spreads by contiguity. The advancing border has a characteristic rolled edge of granulation tissue. Large ulcerations may advance onto the lower abdomen and thighs. Scar formation and healing occur along one border while the opposite border advances.

Superinfection with spirochete-fusiform organisms is common. The ulcer then becomes purulent, painful, foul-smelling, and extremely difficult to treat.

Several therapies are available. Because of the indolent nature of the disease, duration of therapy is relatively long. The following recommended regimens should be given for 3 weeks or until all lesions have healed: azithromycin, 1 g orally once weekly (preferred); doxycycline, 100 mg orally twice daily; or azithromycin, 1 g orally once weekly; or ciprofloxacin, 750 mg orally twice daily; trimethoprim-sulfamethoxazole, 1 double-strength tablet orally twice a day; or erythromycin, 500 mg orally four times a day.

O'Farrell N et al. 2016 European guideline on donovanosis. Int J STD AIDS. 2016;27:605. [PMID: 26882914]

BARTONELLA SPECIES

Bartonella species are responsible for a wide variety of clinical syndromes. **Bacillary angiomatosis**, an important manifestation of bartonellosis, is discussed in Chapter 31. A variety of atypical infections, including retinitis, encephalitis, osteomyelitis, and persistent bacteremia and endocarditis (especially consider in culture-negative endocarditis), have been described.

Trench fever is a self-limited, louse-borne relapsing febrile disease caused by *B. quintana*. The disease has occurred epidemically in louse-infested troops and civilians during wars and endemically in residents of scattered geographic areas (eg, Central America). An urban equivalent of trench fever has been described among persons who are homeless. Humans acquire infection when infected lice feces enter sites of skin breakdown. Onset of symptoms is abrupt and fever lasts 3–5 days, with relapses, although isolated febrile episodes and prolonged fevers can also occur. The patient complains of weakness and severe pain behind the eyes and typically in the back and legs. Lymphadenopathy, splenomegaly, and a transient maculopapular rash may appear. Subclinical infection is frequent, and a carrier state is recognized. The differential diagnosis includes other febrile, self-limited states such as dengue, leptospirosis, malaria, relapsing fever, and typhus. Optimal therapy is uncertain.

Cat-scratch disease is an acute infection of children and young adults caused by *Bartonella henselae*. It is transmitted from cats to humans as the result of a scratch or bite. Within a few days, a papule or ulcer will develop at the inoculation site in one-third of patients. One to 3 weeks later, fever, headache, and malaise occur. Regional lymph nodes become enlarged, often tender, and may suppurate. Lymphadenopathy from cat scratches resembles that due to neoplasm, tuberculosis, lymphogranuloma venereum, and bacterial lymphadenitis. The diagnosis is usually made clinically. Special cultures for bartonellae, serology, or excisional biopsy, though rarely necessary, confirm the diagnosis. The biopsy reveals necrotizing lymphadenitis and is itself not specific for cat-scratch disease. Cat-scratch disease is usually self-limited, requiring no specific therapy. Encephalitis occurs rarely.

Disseminated forms of the disease—bacillary angiomatosis, peliosis hepatitis, and retinitis—occur most commonly in immunocompromised patients such as persons with late stages of HIV or solid organ transplant recipients. The lesions are vasculoproliferative and histopathologically distinct from those of cat-scratch disease. Unexplained fever in patients with late stages of HIV infection is not uncommonly due to bartonellosis. *B. quintana*, the agent of trench fever, can also cause bacillary angiomatosis and persistent bacteremia or endocarditis (which will be “culture-negative” unless specifically sought), the latter two entities being associated with homelessness. Due to the fastidious nature of the organism and its special growth requirements, serologic testing (eg, demonstration of a high antibody titer in an indirect immunofluorescence assay) or nucleic acid amplification tests are often required to establish a diagnosis.

The disseminated forms of the disease (bacillary angiomatosis, peliosis hepatitis, and retinitis) require a prolonged course of antibiotic therapy often in combination with a second agent. Bacteremia and endocarditis can be effectively treated with doxycycline (200 mg orally or intravenously in two divided doses per day) plus 2 weeks of either gentamicin (3 mg/kg/day intravenously) or rifampin (600 mg/day orally in two divided doses) followed by doxycycline monotherapy for a total duration of at least 3 months

unless valve surgery has been performed, in which case treatment can be shortened to 6 weeks after valve surgery. Relapse may occur.

Okaro U et al. *Bartonella* species, an emerging cause of blood-culture-negative endocarditis. Clin Microbiol Rev. 2017;30:709. [PMID: 28490579]

ANAEROBIC INFECTIONS

Anaerobic infections tend to be polymicrobial and abscesses are common. Pus and infected tissue often are malodorous. Septic thrombophlebitis and metastatic infection are frequent and may require incision and drainage. Diminished blood supply that favors proliferation of anaerobes because of reduced tissue oxygenation may interfere with the delivery of antimicrobials to the site of anaerobic infection. Cultures, unless carefully collected under anaerobic conditions, may yield negative results.

Important types of infections that are most commonly caused by anaerobic organisms are listed below. Treatment of all these infections consists of surgical exploration and judicious excision in conjunction with administration of antimicrobial drugs.

1. Head & Neck Infections

Prevotella melaninogenica (formerly *Bacteroides melaninogenicus*) and anaerobic spirochetes are commonly involved in periodontal infections. These organisms, fusobacteria, and peptostreptococci may cause chronic sinusitis, peritonsillar abscess, chronic otitis media, and mastoiditis. *F. necrophorum* has been recognized as a common cause of pharyngitis in adolescents and young adults. *F. necrophorum* infection has been associated with septic internal jugular thrombophlebitis (Lemierre syndrome) and causes septic pulmonary embolization. Hygiene, drainage, and surgical debridement are as important in treatment as antimicrobials. Penicillin alone is inadequate treatment for infections from oral anaerobic organisms because of penicillin resistance, usually due to beta-lactamase production. Therefore, ampicillin/sulbac-tam 1.5–3 g intravenously every 6 hours (if parenteral therapy is required), or amoxicillin/clavulanic acid 875 mg/125 mg orally twice daily, or clindamycin can be used (600 mg intravenously every 8 hours or 300 mg orally every 6 hours). Antimicrobial treatment is continued for a few days after symptoms and signs of infection have resolved. Indolent, established infections (eg, mastoiditis or osteomyelitis) may require prolonged courses of therapy, eg, 4–6 weeks or longer.

2. Chest Infections

Usually in the setting of poor oral hygiene and periodontal disease, aspiration of saliva (which contains 10^8 anaerobic organisms per milliliter in addition to aerobes) may lead to necrotizing pneumonia, lung abscess, and empyema. Polymicrobial infection is the rule, and anaerobes—particularly *P. melaninogenica*, fusobacteria, and peptostreptococci—are common etiologic agents. Most pulmonary infections

respond to antimicrobial therapy alone. Percutaneous chest tube or surgical drainage is indicated for empyema.

Clindamycin, 600 mg intravenously once, followed by 300 mg orally every 6–8 hours, is the treatment of choice for these infections. Metronidazole does not cover facultative streptococci, which often are present, and if used, a second agent that is active against streptococci, such as ceftriaxone 1 g intravenously or intramuscularly daily, should be added. Penicillin, 2 million units intravenously every 4 hours, followed by amoxicillin, 500 mg orally every 8 hours, is an alternative; however, penicillin-resistant *Bacteroides fragilis* and *P. melaninogenica* are commonly isolated and have been associated with clinical failures. Moxifloxacin, 400 mg orally or intravenously once daily, may be used. Because these infections respond slowly, a prolonged course of therapy (eg, 4–6 weeks) is generally recommended.

3. Central Nervous System

Anaerobes are a common cause of brain abscess, subdural empyema, or septic CNS thrombophlebitis. The organisms reach the CNS by direct extension from sinusitis, otitis, or mastoiditis or by hematogenous spread from chronic lung infections. Antimicrobial therapy—eg, ceftriaxone, 2 g intravenously every 12 hours, plus metronidazole, 500 mg intravenously every 8 hours—is an important adjunct to surgical drainage. Duration of therapy is 6–8 weeks but should be based on follow-up imaging. Some small multiple brain abscesses can be treated with antibiotics alone without surgical drainage.

4. Intra-Abdominal Infections

In the colon there are up to 10^{11} anaerobes per gram of content—predominantly *B. fragilis*, clostridia, and pepto-streptococci. These organisms play a central role in most intra-abdominal abscesses following trauma to the colon, as well as diverticulitis, appendicitis, perirectal abscess, hepatic abscess, and cholecystitis, often in association with aerobic coliform bacteria. The bacteriology includes anaerobes as well as enteric gram-negative rods and on occasion enterococci. Therapy should be directed both against anaerobes and gram-negative aerobes. Agents that are active against *B. fragilis* include metronidazole, chloramphenicol, moxifloxacin, tigecycline, ertapenem, imipenem, doripenem, ampicillin-sulbactam, ticarcillin-clavulanic acid, and piperacillin-tazobactam. Resistance to cefoxitin, cefotetan, and clindamycin is increasingly encountered. Most third-generation cephalosporins have poor efficacy.

Table 33–6 summarizes the antibiotic regimens for management of moderate to moderately severe infections (eg, patient hemodynamically stable, good surgical drainage possible or established, low APACHE score, no multiple organ failure) and severe infections (eg, major peritoneal soiling, large or multiple abscesses, patient hemodynamically unstable), particularly if drug-resistant organisms are suspected. An effective oral regimen for patients able to take it is presented also.

Table 33–6. Treatment of anaerobic intra-abdominal infections.

Community-onset

Oral therapy

Moxifloxacin 400 mg every 24 hours

Ciprofloxacin 750 mg twice a day or levofloxacin 750 mg once a day **plus** metronidazole 500 mg every 8 hours

Intravenous therapy

Moderate to moderately severe infections:

Ertapenem 1 g intravenously every 24 hours
or

Ceftriaxone 1 g intravenously every 24 hours **plus** metronidazole intravenously or orally, 500 mg every 8 hours. If penicillin allergic, can replace ceftriaxone with ciprofloxacin 400 mg intravenously (or 500 mg orally) every 12 hours.

Severe infections:

Imipenem 0.5 g intravenously every 6–8 hours or meropenem 1 g every 8 hours or doripenem 0.5 g every 8 hours or piperacillin/tazobactam 3.75 g every 6 hours

Health care-associated

Intravenous therapy

Imipenem 0.5 g intravenously every 6–8 hours or meropenem 1 g every 8 hours or doripenem 0.5 g every 8 hours or piperacillin/tazobactam 4.5 g every 6 hours or

Ceftazidime or cefepime 2 g intravenously every 8 hours **plus** metronidazole 500 mg intravenously or orally every 8 hours

5. Female Genital Tract & Pelvic Infections

The normal flora of the vagina and cervix includes several species of *bacteroides*, *peptostreptococci*, group B streptococci, lactobacilli, coliform bacteria, and, occasionally, spirochetes and clostridia. These organisms commonly cause genital tract infections and may disseminate from there.

While salpingitis is often caused by gonococci and chlamydiae, tubo-ovarian and pelvic abscesses are associated with anaerobes in most cases. Postpartum infections may be caused by aerobic streptococci or staphylococci, but anaerobes are often found, and the worst cases of postpartum or postabortion sepsis are associated with clostridia and *bacteroides*. These have a high mortality rate, and treatment requires both antimicrobials directed against anaerobes and coliforms (similar to treatment of anaerobic intra-abdominal infections, Table 33–6) and abscess drainage or early hysterectomy.

6. Bacteremia & Endocarditis

Anaerobic bacteremia usually originates from the gastrointestinal tract, the oropharynx, pressure injuries, or the female genital tract. Endocarditis due to anaerobic and microaerophilic streptococci and *bacteroides* originates from the same sites. Most cases of anaerobic or microaerophilic streptococcal endocarditis can be effectively treated with 12–20 million units of penicillin G intravenously daily for 4–6 weeks, but optimal therapy of other types of anaerobic bacterial endocarditis must rely on laboratory guidance. Propionibacteria, clostridia, and *bacteroides* occasionally cause endocarditis.

7. Skin & Soft Tissue Infections

Anaerobic infections of the skin and soft tissue usually follow trauma, inadequate blood supply, or surgery and are most common in areas that are contaminated by oral or fecal flora. These infections also occur in injection drug users and persons sustaining animal bites. There may be progressive tissue necrosis (Figure 33–5) and a putrid odor.

Several terms, such as bacterial synergistic gangrene, synergistic necrotizing cellulitis, necrotizing fasciitis (see above), and non-clostridial crepitant cellulitis, have been used to classify these infections. Although there are some differences in microbiology among them, their differentiation on clinical grounds alone is difficult. All are mixed infections caused by aerobic and anaerobic organisms and require aggressive surgical debridement of necrotic tissue for cure.

Broad-spectrum antibiotics active against both anaerobes and gram-positive and gram-negative aerobes (eg, vancomycin plus piperacillin-tazobactam) should be instituted empirically and modified by culture results (see Table 30–5). They are given for about a week after progressive tissue destruction has been controlled and the margins of the wound remain free of inflammation.



▲ Figure 33–5. Left foot gangrene, with plantar extension. (Used, with permission, from Dean SM, Satiani B, Abraham WT. *Color Atlas and Synopsis of Vascular Diseases*. McGraw-Hill, 2014.)

Brook I. Spectrum and treatment of anaerobic infections. *J Infect Chemother*. 2016;22:1. [PMID: 26620376]
de Prost N et al. Therapeutic targets in necrotizing soft tissue infections. *Intensive Care Med*. 2017;43:1717. [PMID: 28474117]

ACTINOMYCOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Recent dental infection, abdominal trauma, or intrauterine contraception device placement.
- ▶ Chronic pneumonia or indolent cervicofacial or intra-abdominal abscess.
- ▶ Sinus tract formation.

General Considerations

Actinomyces israelii and other species of *Actinomyces* occur in the normal flora of the mouth and tonsillar crypts. When introduced into traumatized tissue and associated with other anaerobic bacteria, these actinomycetes become pathogens.

The most common site of infection is the cervicofacial area (about 60% of cases). Infection typically follows extraction of a tooth or other trauma. Lesions may develop in the gastrointestinal tract or lungs following ingestion or aspiration of the organism from its endogenous source in the mouth. Interestingly, *T whippelii*, the causative agent of Whipple disease, is an actinomycete and therefore is related to the species that cause actinomycosis.

Clinical Findings

A. Symptoms and Signs

1. Cervicofacial actinomycosis—Cervicofacial actinomycosis develops slowly. The area becomes markedly indurated, and the overlying skin becomes reddish or cyanotic. Abscesses eventually draining to the surface persist for long periods. “Sulfur granules”—masses of filamentous organisms—may be found in the pus. There is usually little pain unless there is secondary infection. Trismus indicates that the muscles of mastication are involved. Radiography may reveal bony involvement. Cervicofacial or thoracic disease may occasionally involve the CNS, most commonly brain abscess or meningitis.

2. Thoracic actinomycosis—Thoracic involvement begins with fever, cough, and sputum production with night sweats and weight loss. Pleuritic pain may be present. Multiple sinuses may extend through the chest wall, to the heart, or into the abdominal cavity. Ribs may be involved. Radiography shows areas of consolidation and in many cases pleural effusion.

3. Abdominal actinomycosis—Abdominal actinomycosis usually causes pain in the ileocecal region, spiking fever and chills, vomiting, and weight loss; it may be confused

with Crohn disease. Irregular abdominal masses may be palpated. Pelvic inflammatory disease caused by actinomycetes has been associated with prolonged use of an intrauterine contraceptive device. Sinuses draining to the exterior may develop. CT scanning reveals an inflammatory mass extended to involve bone.

B. Laboratory Findings

The anaerobic, gram-positive organism may be demonstrated as a granule or as scattered branching gram-positive filaments in the pus. Anaerobic culture is necessary to distinguish actinomycetes from *Nocardia* species because specific therapy differs for the two infections. Histopathology examination of affected tissue and bone is useful in identifying organisms that are fastidious and slow to culture.

Treatment

Penicillin G is the drug of choice. Ten to 20 million units are given intravenously for 4–6 weeks, followed by oral penicillin V, 500 mg four times daily. Alternatives include ampicillin, 12 g/day intravenously for 4–6 weeks, followed by oral amoxicillin, 500 mg three times daily, or doxycycline, 100 mg twice daily intravenously or orally. Response to therapy is slow. Therapy should be continued for weeks to months after clinical manifestations have disappeared to ensure cure. Surgical procedures such as drainage and resection may be beneficial. With penicillin and surgery, the prognosis is good. The difficulties of diagnosis, however, may permit extensive destruction of tissue before the diagnosis is identified and therapy is started.

Xu Y et al. Disseminated actinomycosis. N Engl J Med. 2018; 379:1071. [PMID: 30207906]

NOCARDIOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Indolent pneumonia with dissemination to CNS, skin, and bone or primary cutaneous disease.
- ▶ Suspect in setting of chronic lung disease or immunocompromised person.

General Considerations

Nocardia species are aerobic filamentous soil bacteria that can cause pulmonary and systemic nocardiosis. Common *Nocardia* species include members of the *Nocardia asteroides* complex and *Nocardia brasiliensis*. Bronchopulmonary abnormalities (eg, bronchiectasis) predispose to colonization, but infection is unusual unless the patient is also receiving systemic corticosteroids or is otherwise immunosuppressed.

Clinical Findings

Pulmonary involvement usually begins with malaise, loss of weight, fever, and night sweats. Cough and production of purulent sputum are the chief complaints. Pulmonary infiltrates may penetrate to the exterior through the chest wall, invading the ribs.

Dissemination involves any organ. Brain abscesses and subcutaneous nodules are most frequent. Cutaneous lesions may mimic actinomycosis. Radiography may show infiltrates accompanied by pleural effusion. Even in the absence of clinical symptoms and signs of CNS infection, clinicians should consider brain imaging in patients with nocardiosis to rule out an occult abscess.

Nocardia species are usually found as delicate, branching, gram-positive filaments. They may be weakly acid-fast, occasionally causing diagnostic confusion with tuberculosis. Identification is made by culture.

Treatment

For isolated primary cutaneous infections, therapy is initiated with trimethoprim-sulfamethoxazole orally or intravenously (5–10 mg/kg/day based on trimethoprim). Surgical procedures such as drainage and resection may be needed as adjunctive therapy for isolated cutaneous disease. A higher dose of 15 mg/kg/day (based on trimethoprim) should be used for disseminated or pulmonary infections. Resistance to trimethoprim-sulfamethoxazole is increasing and initiating treatment with two drugs while awaiting antibiotic susceptibilities in cases of disseminated or severe localized disease should be considered. Brain abscesses or pneumonia should be initially treated with combination therapy. Alternative agents or drugs that can be given in combination with trimethoprim-sulfamethoxazole include imipenem, 500 mg intravenously every 6 hours; amikacin, 7.5 mg/kg intravenously every 12 hours; or minocycline, 100–200 mg orally or intravenously twice daily. Consultation with an infectious diseases expert is encouraged.

Response may be slow; therapy should be continued for at least 6 months. The prognosis in systemic nocardiosis is poor when diagnosis and therapy are delayed.

Fatahi-Bafghi M. Nocardiosis from 1888 to 2017. Microb Pathog. 2018;114:369. [PMID: 29146497]

Takiguchi Y et al. Pulmonary nocardiosis: a clinical analysis of 30 cases. Intern Med. 2017;56:1485. [PMID: 28626172]

INFECTIONS CAUSED BY MYCOBACTERIA

NONTUBERCULOUS MYCOBACTERIAL DISEASES

About 10% of mycobacterial infections are caused by nontuberculous mycobacteria. Nontuberculous mycobacterial infections are among the most common opportunistic infections in advanced HIV disease. These organisms have distinctive laboratory characteristics, occur ubiquitously in the environment, are not communicable from person to person, and are often resistant to standard antituberculous drugs.

1. Pulmonary Infections

Mycobacterium avium complex (MAC) causes a chronic, slowly progressive pulmonary infection resembling tuberculosis in immunocompetent patients who typically have underlying pulmonary disease. Susceptibility testing for macrolide-resistance should be performed on clinical isolates. Pulmonary disease is often classified as nodular, bronchiectatic, or fibrocavitory. Treatment of pulmonary MAC requires a three-drug regimen: clarithromycin (500–1000 mg orally daily) or azithromycin (500 mg orally daily) plus either rifampin (600 mg orally daily) or rifabutin (300 mg orally daily) plus ethambutol (15 mg/kg orally daily). Therapy is continued for at least 12 months after sterilization of cultures.

M. kansasi can produce clinical disease resembling tuberculosis, but the illness progresses more slowly. Most such infections occur in patients with preexisting lung disease, though 40% of patients have no known pulmonary disease. Microbiologically, *M. kansasi* is similar to *M. tuberculosis* and is sensitive to the same drugs except pyrazinamide, to which it is resistant. Therapy with isoniazid, ethambutol, and rifampin for 2 years (or 1 year after sputum conversion) has been successful.

Less common causes of pulmonary disease include *M. xenopi*, *M. szulgai*, and *M. gordona*. These organisms have variable sensitivities, and treatment is based on results of sensitivity tests. The rapidly growing mycobacteria, *M. abscessus*, *M. chelonae*, and *M. fortuitum*, also can cause pneumonia in the occasional patient.

Daley CL et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis. 2020;71:905. [PMID: 32797222]

Jarand J et al. Long-term follow-up of *Mycobacterium avium* complex lung disease in patients treated with regimens including clofazimine and/or rifampin. Chest. 2016;149:1285. [PMID: 26513209]

2. Lymphadenitis

Most cases of lymphadenitis (scrofula) in adults are caused by *M. tuberculosis* and can be a manifestation of disseminated disease. In children, the majority of cases are due to nontuberculous mycobacterial species. Infection with nontuberculous mycobacteria can be successfully treated by surgical excision without antituberculous therapy.

3. Skin & Soft Tissue Infections

Skin and soft tissue infections such as abscesses, septic arthritis, and osteomyelitis can result from direct inoculation or hematogenous dissemination or may occur as a complication of surgery.

M. abscessus, *M. chelonae*, and *M. fortuitum* are frequent causes of these types of infections. Most cases occur in the extremities and initially present as nodules. Ulceration with abscess formation often follows. The organisms are resistant

to the usual antituberculosis drugs and may have susceptibility to clarithromycin, azithromycin, doxycycline, amikacin, cefoxitin, sulfonamides, imipenem, and ciprofloxacin. Given the multidrug-resistant nature of these organisms, obtaining antibiotic susceptibility testing is recommended. Therapy often includes surgical debridement along with at least two active antibiotics. Antibiotic therapy is usually continued for 3 months, although this must be determined based on clinical response.

M. marinum infection (“swimming pool granuloma”) presents as a nodular skin lesion following exposure to nonchlorinated water. The lesions respond to therapy with clarithromycin, doxycycline, minocycline, or trimethoprim-sulfamethoxazole.

M. ulcerans infection (Buruli ulcer) is seen mainly in Africa and Australia and produces a large ulcerative lesion. Therapy consists of surgical excision and skin grafting.

4. Disseminated *Mycobacterium avium* Infection

MAC causes disseminated disease in immunocompromised patients, most commonly in patients in the late stages of HIV infection, when the CD4 cell count is less than 50/mcL (see Pulmonary Disease Caused by Nontuberculous Mycobacteria, Chapter 9, for a discussion of the infection in immunocompetent persons). Persistent fever and weight loss are the most common symptoms. The organism can usually be cultured from multiple sites, including blood, liver, lymph node, or bone marrow. Blood culture is the preferred means of establishing the diagnosis and has a sensitivity of 98%.

Agents with proved activity against MAC are rifabutin, azithromycin, clarithromycin, and ethambutol. Amikacin and ciprofloxacin work in vitro, but clinical results are inconsistent. A combination of two or more active agents should be used to prevent rapid emergence of secondary resistance. Clarithromycin, 500 mg orally twice daily, plus ethambutol, 15 mg/kg/day orally as a single dose, with or without rifabutin, 300 mg/day orally, is the treatment of choice. Azithromycin, 500 mg orally once daily, may be used instead of clarithromycin. Insufficient data are available to permit specific recommendations about second-line regimens for patients intolerant of macrolides or those with macrolide-resistant organisms. MAC therapy may be discontinued in patients who have been treated with 12 months of therapy for disseminated MAC, who have no evidence of active disease, and whose CD4 counts exceed 100 cells/mcL for 6 months while receiving antiretroviral therapy (ART).

Antimicrobial prophylaxis of MAC prevents disseminated disease and prolongs survival. It is the standard of care to offer it to all HIV-infected patients with CD4 counts of 50/mcL or less. In contrast to active infection, single-drug oral regimens of clarithromycin, 500 mg twice daily, azithromycin, 1200 mg once weekly, or rifabutin, 300 mg once daily, are appropriate. Clarithromycin or azithromycin is more effective and better tolerated than rifabutin, and therefore preferred. Primary prophylaxis for MAC infection can be stopped in patients who have responded to

antiretroviral combination therapy with elevation of CD4 counts of greater than 100 cells/mcL for 3 months.

Masur H et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: updated guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;58:1308. [PMID: 24585567]

MYCOBACTERIUM TUBERCULOSIS INFECTIONS

Tuberculosis is discussed in Chapter 9. Further information and expert consultation can be obtained from the Curry International Tuberculosis Center at the website www.currytbccenter.ucsf.edu or by telephone, 510-238-5100.

TUBERCULOUS MENINGITIS



ESSENTIALS OF DIAGNOSIS

- ▶ Gradual onset of listlessness and anorexia.
- ▶ Headache, vomiting, and seizures common.
- ▶ Cranial nerve abnormalities typical.
- ▶ Tuberculosis focus may be evident elsewhere.
- ▶ Cerebrospinal fluid shows several hundred lymphocytes, low glucose, and high protein.

General Considerations

Tuberculous meningitis is caused by rupture of a meningeal tuberculoma resulting from earlier hematogenous seeding of tubercle bacilli from a pulmonary focus, or it may be a consequence of miliary spread.

Clinical Findings

A. Symptoms and Signs

The onset is usually gradual, with listlessness, irritability, anorexia, and fever, followed by headache, vomiting, convulsions, and coma. In older patients, headache and behavioral changes are prominent early symptoms. Nuchal rigidity and cranial nerve palsies occur as the meningitis progresses. Evidence of active tuberculosis elsewhere or a history of prior tuberculosis is present in up to 75% of patients.

B. Laboratory Findings

The spinal fluid is frequently yellowish, with increased pressure, 100–500 cells/mcL ($0.1\text{--}0.5 \times 10^9/\text{L}$) (predominantly lymphocytes, though neutrophils may be present early during infection), increased protein, and decreased glucose. Acid-fast stains of cerebrospinal fluid are often

negative, and cultures also may be negative in 15–25% of cases. Nucleic acid amplification tests for rapid diagnosis of tuberculosis have variable sensitivity and specificity and none are FDA approved for use in meningitis. Chest radiographs often reveal abnormalities compatible with tuberculosis but may be normal. The tuberculin skin test is usually (but not always) positive.

Differential Diagnosis

Tuberculous meningitis may be confused with any other type of meningitis, but the gradual onset, the predominantly lymphocytic pleocytosis of the spinal fluid, and evidence of tuberculosis elsewhere often point to the diagnosis. Fungal and other granulomatous meningitides, syphilis, and carcinomatous meningitis are in the differential diagnosis.

Complications

Complications of tuberculous meningitis include seizures, cranial nerve palsies, stroke, and obstructive hydrocephalus with impaired cognitive function. These result from inflammatory exudate primarily of the basilar meninges and arteries.

Treatment

Presumptive diagnosis followed by early, empiric antituberculous therapy is essential for survival and to minimize sequelae. Even if cultures are not positive, a full course of therapy is warranted if the clinical setting is suggestive of tuberculous meningitis.

Regimens that are effective for pulmonary tuberculosis are effective also for tuberculous meningitis (see Table 9–15). Rifampin, isoniazid, and pyrazinamide all penetrate well into cerebrospinal fluid. The penetration of ethambutol is more variable, but therapeutic concentrations can be achieved, and the drug has been successfully used for meningitis. Aminoglycosides penetrate less well. Regimens that do not include both isoniazid and rifampin may be effective but are less reliable and generally must be given for longer periods.

Many authorities recommend the addition of corticosteroids for patients with focal deficits or altered mental status. Dexamethasone, 0.15 mg/kg intravenously or orally four times daily for 1–2 weeks, then discontinued in a tapering regimen over 4 weeks, may be used.

Heemskerk AD et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016; 374:124. [PMID: 26760084]

Khonga M et al. Xpert MTB/RIF Ultra: a gamechanger for tuberculous meningitis? *Lancet Infect Dis*. 2018;18:6. [PMID: 28919337]

Prasad K et al. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4:CD002244. [PMID: 27121755]

INFECTIONS CAUSED BY CHLAMYDIAE

CHLAMYDIA TRACHOMATIS INFECTIONS

1. Lymphogranuloma Venereum

ESSENTIALS OF DIAGNOSIS

- ▶ Evanescent primary genital lesion.
- ▶ Inguinal buboes with suppuration and draining sinuses.
- ▶ Proctitis and rectal stricture in women or in men who have sex with men.
- ▶ Positive complement fixation test.

General Considerations

Lymphogranuloma venereum (LGV) is an acute and chronic sexually transmitted disease caused by *C trachomatis* types L1–L3. The disease is acquired during intercourse or through contact with contaminated exudate from active lesions. The incubation period is 5–21 days. After the genital lesion disappears, the infection spreads to the lymph nodes of the genital and rectal areas. Inapparent infections and latent disease are not uncommon.

Clinical Findings

A. Symptoms and Signs

In men, the initial vesicular or ulcerative lesion (on the external genitalia) is evanescent and often goes unnoticed. Inguinal buboes appear 1–4 weeks after exposure, are often bilateral, and have a tendency to fuse, soften, and break down to form multiple draining sinuses, with extensive scarring. **In women**, the genital lymph drainage is to the perirectal glands. Early anorectal manifestations are proctitis with tenesmus and bloody purulent discharge; late manifestations are chronic cicatrizing inflammation of the rectal and perirectal tissue. These changes lead to obstipation and rectal stricture and, occasionally, rectovaginal and perianal fistulas. They are also seen with anal coitus.

B. Laboratory Findings

The complement fixation antibody testing may be positive (titers greater than 1:64), but cross-reaction with other chlamydiae occurs. Although a positive reaction may reflect remote infection, high titers usually indicate active disease. Nucleic acid detection tests are sensitive but cannot differentiate LGV from non-LGV strains.

Differential Diagnosis

The early lesion of LGV must be differentiated from the lesions of syphilis, genital herpes, and chancroid; lymph node involvement must be distinguished from that due to tularemia, tuberculosis, plague, neoplasm, or pyogenic infection; and rectal stricture must be distinguished from that due to neoplasm and ulcerative colitis.

Treatment

If diagnostic testing for LGV is not available, patients with a clinical presentation suggestive of LGV should be treated empirically. The antibiotic of choice is doxycycline (contraindicated in pregnancy), 100 mg orally twice daily for 21 days. Erythromycin, 500 mg orally four times a day for 21 days, is also effective. Azithromycin, 1 g orally once weekly for 3 weeks, may also be effective.

De Vries HJC et al. 2019 European guideline on the management of lymphogranuloma venereum. *J Eur Acad Dermatol Venereol*. 2019;33:1821. [PMID: 31243838]

Workowski KA et al; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64:1. [PMID: 26042815]

2. Chlamydial Urethritis & Cervicitis

ESSENTIALS OF DIAGNOSIS

- ▶ *C trachomatis*: common cause of urethritis, cervicitis, and postgonococcal urethritis.
- ▶ Diagnosis made by nucleic acid amplification of urine or swab specimen.

General Considerations

C trachomatis immunotypes D–K are isolated in about 50% of cases of nongonococcal urethritis and cervicitis. In other cases, *Ureaplasma urealyticum* or *Mycoplasma genitalium* can be grown as a possible etiologic agent. *C trachomatis* is an important cause of postgonococcal urethritis. Coinfection with gonococci and chlamydiae is common, and postgonococcal (ie, chlamydial) urethritis may persist after successful treatment of the gonococcal component. Occasionally, epididymitis, prostatitis, or proctitis is caused by chlamydial infection. Chlamydiae are a leading cause of infertility in females in the United States.

Clinical Findings

A. Symptoms and Signs

The urethral or cervical discharge due to *C trachomatis* tends to be less painful, less purulent, and watery compared with gonococcal infection. Women infected with chlamydiae may be asymptomatic or may have symptoms and signs of cervicitis, salpingitis, or pelvic inflammatory disease. Long-term sequelae may include ectopic pregnancy and infertility.

B. Laboratory Findings

A patient with clinical signs and symptoms of urethritis or cervicitis is assumed to have chlamydial infection until proven otherwise. The diagnosis should be confirmed, whenever possible, by the FDA-approved, highly sensitive nucleic acid amplification tests for use with urine or vaginal swabs. A negative urine nucleic acid amplification test

for chlamydia reliably excludes the diagnosis of chlamydial urethritis or cervicitis and therapy need not be administered. Urine testing does not exclude infection at other sites, such as rectal or pharyngeal disease.

C. Screening

Active screening for chlamydial infection is recommended in certain settings: pregnant women; all sexually active women 25 years of age and under; older women with risk factors for sexually transmitted diseases; and men with risk factors for sexually transmitted diseases, such as HIV-positive men or men who have sex with men.

Treatment

Recommended regimens are a single oral 1-g dose of azithromycin (preferred and safe in pregnancy), 100 mg of doxycycline orally for 7 days (contraindicated in pregnancy), or 500 mg of levofloxacin once daily for 7 days (also contraindicated in pregnancy). Presumptively administered therapy still may be indicated for some patients, such as for an individual with gonococcal infection in whom no chlamydial testing was performed or a test other than a nucleic acid amplification test was used to exclude the diagnosis, or an individual for whom a test result is pending but is considered unlikely to follow up, and for sexual contacts of documented cases. As for all patients in whom sexually transmitted diseases are diagnosed, studies for HIV and syphilis should also be performed.

Geisler WM et al. Azithromycin versus doxycycline for urogenital *Chlamydia trachomatis* infection. *N Engl J Med*. 2015;373:2512. [PMID: 26699167]

Wiesenfeld HC. Screening for *Chlamydia trachomatis* infections in women. *N Engl J Med*. 2017;376:765. [PMID: 28225683]

Workowski KA et al; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64:1. [PMID: 26042815]

CHLAMYDOPHILA PSITTACI & PSITTACOSIS (Ornithosis)



ESSENTIALS OF DIAGNOSIS

- ▶ Fever, chills, and cough; headache common.
- ▶ Atypical pneumonia with slightly delayed appearance of signs of pneumonitis.
- ▶ Contact with infected bird (psittacine, pigeons, many others) 7–15 days previously.
- ▶ Isolation of chlamydiae or rising titer of complement-fixing antibodies.

General Considerations

Psittacosis is acquired from contact with birds (parrots, parakeets, pigeons, chickens, ducks, and many others), which may or may not be ill. The history may be difficult

to obtain if the patient acquired infection from an illegally imported bird.

Clinical Findings

The onset is usually rapid, with fever, chills, myalgia, dry cough, and headache. Signs include temperature-pulse dissociation, dullness to percussion, and rales. Pulmonary findings may be absent early. Dyspnea and cyanosis may occur later. Endocarditis, which is culture-negative, may occur. The radiographic findings in typical psittacosis are those of atypical pneumonia, which tends to be interstitial and diffuse in appearance, though consolidation can occur. Psittacosis is indistinguishable from other bacterial or viral pneumonias by radiography.

The organism is rarely isolated from cultures. The diagnosis is usually made serologically; antibodies appear during the second week and can be demonstrated by complement fixation or immunofluorescence. Antibody response may be suppressed by early chemotherapy.

Differential Diagnosis

The illness is indistinguishable from viral, mycoplasmal, or other atypical pneumonias except for the history of contact with birds. Psittacosis is in the differential diagnosis of culture-negative endocarditis.

Treatment

Treatment consists of tetracycline, 0.5 g orally every 6 hours or 0.5 g intravenously every 12 hours, for 14–21 days. Erythromycin, 500 mg orally every 6 hours, may be effective as well.

Hogerwerf L et al. *Chlamydia psittaci* (psittacosis) as a cause of community-acquired pneumonia: a systematic review and meta-analysis. *Epidemiol Infect*. 2017;145:3096. [PMID: 28946931]

CHLAMYDOPHILA PNEUMONIAE INFECTION

C pneumoniae causes pneumonia and bronchitis. The clinical presentation of pneumonia is that of an atypical pneumonia. The organism accounts for approximately 10% of community-acquired pneumonias, ranking second to *mycoplasma* as an agent of atypical pneumonia.

Like *C psittaci*, strains of *C pneumoniae* are resistant to sulfonamides. Azithromycin, 500 mg orally on day 1 and 250 mg for 4 more days, or doxycycline, 100 mg orally two times a day for 10 days, appears to be effective therapy. Fluoroquinolones, such as levofloxacin (500 mg orally once daily for 7–14 days) or moxifloxacin (400 mg orally once daily for 7–14 days), are active in vitro against *C pneumoniae* and probably are effective. It is unclear if empiric coverage for atypical pathogens in hospitalized patients with community-acquired pneumonia provides a survival benefit or improves clinical outcome.

Fujita J et al. Where is *Chlamydophila pneumoniae* pneumonia? *Respir Investig*. 2020;58:336. [PMID: 32703757]

34

Spirochetal Infections

Susan S. Philip, MD, MPH

SYPHILIS

NATURAL HISTORY & PRINCIPLES OF DIAGNOSIS & TREATMENT

Syphilis is a complex infectious disease caused by *Treponema pallidum*, a spirochete capable of infecting almost any organ or tissue in the body and causing protean clinical manifestations (Table 34-1). Transmission occurs most frequently during sexual contact (including oral sex) or via the placenta from mother to fetus (congenital syphilis). The risk of acquiring syphilis after unprotected sex with an individual with infectious syphilis is approximately 30–50%. Rarely, it can also be transmitted through non-sexual contact or blood transfusion. The natural history of acquired syphilis is generally divided into two major stages: early (infectious) syphilis and late syphilis.

Early infectious syphilis includes primary lesions (chancre and regional lymphadenopathy) appearing during primary syphilis, secondary lesions (commonly involving skin and mucous membranes, occasionally bone, central nervous system [CNS], or liver) appearing during secondary syphilis (when dissemination of *T pallidum* produces systemic signs), relapsing lesions during early latency, and congenital lesions. The hallmark of these lesions is an abundance of spirochetes; tissue reaction is usually minimal.

Late (tertiary) syphilis consists of so-called benign (gummatus) lesions involving skin, bones, and viscera; cardiovascular disease (principally aortitis); and a variety of CNS and ocular syndromes. These forms of syphilis are not contagious. The lesions contain few demonstrable spirochetes, but tissue reactivity (vasculitis, necrosis) is severe and suggestive of hypersensitivity phenomena. Between these stages are symptom-free latent phases. In early latent syphilis, which is defined as the symptom-free interval lasting up to 1 year after initial infection, infectious lesions can recur.

Public health efforts to control syphilis focus on the diagnosis and treatment of early (infectious) cases and their partners.

Most cases of syphilis in the United States continue to occur in men who have sex with men (MSM). Globally, the World Health Organization (WHO) estimates 5.6 million total incident syphilis infections occur annually, with a

prevalence of 1% among pregnant women attending antenatal clinics. Preventing congenital syphilis is a major public health goal for the Centers for Disease Control and Prevention (CDC) and WHO.

COURSE & PROGNOSIS

The lesions associated with primary and secondary syphilis are self-limiting, even without treatment, and resolve with few or no residua. Ocular and otologic syphilis have been associated with permanent vision and hearing loss. Tertiary and congenital syphilis may be highly destructive and permanently disabling and may lead to death. While infection is almost never completely eradicated in the absence of treatment, most infections likely remain latent without sequelae, and only a small number of latent infections progress to further disease.

CLINICAL STAGES OF SYPHILIS

1. Primary Syphilis



ESSENTIALS OF DIAGNOSIS

- ▶ Painless ulcer on genitalia, perianal area, rectum, pharynx, tongue, lip, or elsewhere.
- ▶ Fluid expressed from ulcer contains *T pallidum* by immunofluorescence or darkfield microscopy.
- ▶ Nontender enlargement of regional lymph nodes.
- ▶ Serologic nontreponemal and treponemal tests may be positive.

Clinical Findings

A. Symptoms and Signs

The typical lesion is the chancre at the site or sites of inoculation, most frequently located on the penis (Figure 34-1), labia, cervix, or anorectal region. Anorectal lesions are especially common among MSM. Chancres also occur occasionally in the oropharynx (lip, tongue, or tonsil) and

Table 34–1. Stages of syphilis and common clinical manifestations.

Primary syphilis	
Chancre:	painless ulcer with clean base and firm indurated borders
Regional lymphadenopathy	
Secondary syphilis	
Skin and mucous membranes	
Rash:	diffuse (may include palms and soles), macular, papular, pustular, and combinations
Condylomata lata	
Mucous patches:	painless, silvery ulcerations of mucous membrane with surrounding erythema
Generalized lymphadenopathy	
Constitutional symptoms	
Fever, usually low-grade	
Malaise, anorexia	
Arthralgias and myalgias	
Central nervous system	
Asymptomatic	
Symptomatic	
Meningitis	
Cranial neuropathies (II–VIII)	
Other	
Ocular: iritis, iridocyclitis	
Renal: glomerulonephritis, nephrotic syndrome	
Hepatitis	
Musculoskeletal: arthritis, periostitis	
Tertiary syphilis	
Late benign (gummatous):	granulomatous lesion usually involving skin, mucous membranes, and bones but any organ can be involved
Cardiovascular	
Aortic regurgitation	
Coronary ostial stenosis	
Aortic aneurysm	
Neurosyphilis	
Asymptomatic	
Meningovascular	
Tabes dorsalis	
General paresis	

Note: Central nervous system involvement may occur at any stage.

rarely on the breast or finger or elsewhere. An initial small erosion appears 10–90 days (average, 3–4 weeks) after inoculation then rapidly develops into a painless superficial ulcer with a clean base and firm, indurated margins. This is associated with enlargement of regional lymph nodes, which are rubbery, discrete, and nontender. Healing of the chancre occurs without treatment, but a scar may form, especially with secondary bacterial infection. Multiple chancres may be present, particularly in HIV-positive patients. Although the “classic” ulcer of syphilis has been described as nontender, nonpurulent, and indurated, only 31% of patients have this triad.

B. Laboratory Findings

1. Microscopic examination—In early syphilis, darkfield microscopic examination by a skilled observer of fresh exudate from moist lesions or material aspirated from



▲ Figure 34–1. Primary syphilis with a large chancre on the glans of the penis. The multiple small surrounding ulcers are part of the syphilis and not a second disease. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

regional lymph nodes is up to 90% sensitive for diagnosis but is usually only available in select clinics that specialize in sexually transmitted infections.

An immunofluorescent staining technique for demonstrating *T pallidum* in dried smears of fluid taken from early syphilitic lesions is performed in only a few laboratories.

T pallidum polymerase chain reaction (PCR) is available in select research, referral, and public health laboratories and has the highest yield in primary and secondary lesions. Organisms can also be detected in blood, especially in congenital and secondary syphilis cases.

2. Serologic tests for syphilis—(Table 34–2.) Serologic tests (the mainstay of syphilis diagnosis) fall into two general categories: (1) Nontreponemal tests detect antibodies to lipoidal antigens present in the host after modification

Table 34–2. Percentage of patients with positive serologic tests for syphilis.¹

Test	Stage		
	Primary	Secondary	Tertiary
VDRL or RPR	75–85%	99–100%	40–95%
FTA-ABS, TPPA, or MHA-TP	69–100%	100%	94–98%
MHA-TP	46–89%	90–100%	NA
EIA or CIA	54–100%	100%	NA

¹Based on untreated cases.

CIA, chemiluminescence assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; MHA-TP, microhemagglutination assay for *T pallidum*; RPR, rapid plasma reagent test; TPPA, *T pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory test.

by *T pallidum*. (2) Treponemal tests use live or killed *T pallidum* as antigen to detect antibodies specific for pathogenic treponemes.

A. NONTREPONEMAL ANTIBODY TESTS—The most commonly used nontreponemal antibody tests are the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagins (RPR) tests. A different, enzyme immunoassay (EIA)-based screening algorithm is discussed below.

Nontreponemal tests generally become positive 4–6 weeks after infection or 1–3 weeks after the appearance of a primary lesion; they are almost invariably positive in the secondary stage. These tests are nonspecific and may be positive in patients with non-sexually transmitted treponematoses. More important, false-positive serologic reactions are frequently encountered in a wide variety of conditions, including autoimmune diseases, infectious mononucleosis, malaria, febrile diseases, leprosy, injection drug use, infective endocarditis, advanced age, hepatitis C viral infection, and pregnancy. False-positive nontreponemal tests are usually of low titer and transient and may be distinguished from true positives by correlating with clinical findings and performing a treponemal specific antibody test. False-negative results can be seen when very high antibody titers are present (**the prozone phenomenon**). If syphilis is strongly suspected and the nontreponemal test is negative, the laboratory should be instructed to dilute the specimen to detect a positive reaction.

Nontreponemal antibody titers are used to monitor the response to therapy and should decline over time. The rate of decline depends on various factors. In general, persons with repeat infections, higher initial titers, more advanced stages of disease, or who are HIV-infected at the time of treatment have a slower seroconversion rate and are more likely to remain serofast (ie, titers decline but do not become nonreactive). The RPR and VDRL tests are equally reliable, but RPR titers tend to be higher than VDRL titers. Thus, when these tests are used to follow disease activity, the same testing method should be used and preferably performed at the same laboratory.

B. TREPONEMAL ANTIBODY TESTS—These tests measure antibodies capable of reacting with *T pallidum* antigens. The *T pallidum* particle agglutination (TPPA) test and the fluorescent treponemal antibody absorption test (FTA-ABS) are two of the most commonly used treponemal tests. Newer treponemal tests used in reverse screening algorithms include the EIA and chemiluminescence assay (CIA).

In the traditional screening algorithm, the treponemal tests are used to confirm a positive nontreponemal test. Because of their sensitivity, particularly in the late stages of the disease, treponemal tests are also of value when there is clinical evidence of syphilis, but the nontreponemal serologic test for syphilis is negative. Treponemal tests are reactive in many patients with primary syphilis and in almost all patients with secondary syphilis (Table 34–2). Although a reactive treponemal-specific serologic test remains reactive throughout a patient's life in most cases, it may (like nontreponemal antibody tests) revert to negative with adequate therapy. Final decisions about the significance of the results

of serologic tests for syphilis must be based on a total clinical appraisal and may require expert consultation.

C. ENZYME IMMUNOASSAY (EIA)- OR CHEMILUMINESCENCE IMMUNOASSAY (CIA)-BASED SCREENING ALGORITHMS—

Newer screening algorithms reverse the traditional test order and begin with an automated treponemal antibody test (eg, EIA or CIA) and then follow up with a nontreponemal test (RPR or VDRL) if the treponemal test is positive. This algorithm is faster and decreases labor costs to laboratories when compared with traditional screening. The EIAs have sensitivities of 95–100% and specificities of 99–100%.

The reverse algorithms can cause challenges in clinical management. A positive treponemal test with a negative RPR or VDRL may represent prior, treated syphilis; untreated latent syphilis; or a false-positive treponemal test. Such results should be evaluated with a second, different treponemal test as a “tie-breaker.” Reverse algorithms are recommended by several international organizations including the International Union against Sexually Transmitted Infections (IUSTI), but the CDC still recommends the traditional algorithm.

D. RAPID TREPONEMAL TESTS—Both a treponemal and a dual HIV/treponemal rapid point of care test are approved for use in the United States. Other tests are available internationally and are commonly used in limited-resource settings. Sensitivity ranges from 62% to 100% and specificity from 83% to 95%.

3. Polymerase chain reaction—In the United States, there are no commercially available FDA-approved *T pallidum* PCR test kits. However, kits are available as a laboratory-developed test in select research, referral, and public health laboratories and have the highest yield in primary and secondary lesions. There are no standards for these tests, but PCR has many advantages as a tool for direct detection, including high sensitivity and ability to use a wide range of clinical specimen types, including cerebrospinal fluid. PCR testing of blood has low sensitivity and is not recommended.

4. Cerebrospinal fluid examination (CSF)—See Neurosyphilis section.

► Differential Diagnosis

The syphilitic chancre may be confused with genital herpes, chancroid (usually painful and uncommon in the United States), lymphogranuloma venereum, or neoplasm. Simultaneous evaluation for herpes simplex virus types 1 and 2 using PCR or culture should also be done in these cases.

► Prevention & Screening

Avoidance of sexual contact is the only completely reliable method of prevention but is an impractical public health measure. Latex or polyurethane condoms are effective but protect covered areas only. Men who have sex with men should be screened every 6–12 months, and as often as every 3 months in high-risk individuals (those who have multiple encounters with anonymous partners or who have sex in conjunction with the use of drugs). Every pregnant

woman should be screened at the first prenatal visit and in some states with increasing congenital syphilis rates, again in the third trimester. A third screening at delivery is recommended if there are risk indicators, including poverty, sex work, illicit drug use, history of other sexually transmitted diseases, and residence in a community with high syphilis morbidity. Patients treated for other sexually transmitted diseases should also be tested for syphilis, and persons who have known or suspected sexual contact with patients who have syphilis should be evaluated and presumptively treated to abort development of infectious syphilis (see Treating Syphilis Contacts below).

Treatment

A. Antibiotic Therapy

Penicillin remains the preferred treatment for syphilis, since there have been no documented cases of penicillin-resistant *T pallidum* (Table 34–3). In pregnant women, penicillin is the only option that reliably treats the fetus (see below).

Alternatives to penicillin for nonpregnant patients include doxycycline and ceftriaxone (although optimum dose and duration for ceftriaxone are not well defined). Azithromycin has been shown to be effective in some parts

of the world but should be used with caution; it should not be used at all in MSM due to demonstrated resistance. All patients treated with a non-penicillin regimen must have particularly close clinical and serologic follow-up.

B. Managing Jarisch–Herxheimer Reaction

The Jarisch–Herxheimer reaction, manifested by fever and aggravation of the existing clinical picture in the hours following treatment, is a cytokine-mediated immunologic reaction to endotoxins released from the killed bacteria. It is most common in early syphilis, particularly secondary syphilis where it can occur in 66% of cases.

The reaction may be blunted by simultaneous administration of antipyretics, although no proven method of prevention exists. In cases with increased risk of morbidity due to the Jarisch–Herxheimer reaction (including CNS or cardiac involvement and pregnancy), consultation with an infectious disease expert is recommended. Patients should be reminded that the reaction does not signify an allergy to penicillin.

C. Local Measures (Mucocutaneous Lesions)

Local treatment is usually not necessary. No local antiseptics or topical antibiotics should be applied to a lesion until specimens for microscopy have been obtained.

Table 34–3. Recommended treatment for syphilis.¹

Stage of Syphilis	Treatment	Alternative ²	Comment
Early			
Primary, secondary, or early latent	Benzathine penicillin G 2.4 million units intramuscularly once	Doxycycline 100 mg orally twice daily for 14 days or Tetracycline 500 mg orally four times daily for 14 days or Ceftriaxone 1 g intramuscularly or intravenously daily for 8–10 days ³	
Late			
Late latent or uncertain duration	Benzathine penicillin G 2.4 million units intramuscularly weekly for 3 weeks	Doxycycline 100 mg orally twice daily for 28 days or Tetracycline 500 mg orally four times daily for 28 days	No routine CSF evaluation needed unless neurologic, otologic, or ocular changes
Tertiary without neurosyphilis	Benzathine penicillin G 2.4 million units intramuscularly weekly for 3 weeks	Doxycycline 100 mg orally twice daily for 28 days or Tetracycline 500 mg orally four times daily for 28 days	CSF evaluation recommended in all patients
Neurosyphilis	Aqueous penicillin G 18–24 million units intravenously daily, given every 3–4 hours or as continuous infusion for 10–14 days	Procaine penicillin, 2.4 million units intramuscularly daily with probenecid 500 mg orally four times daily for 10–14 days or Ceftriaxone 2 g intramuscularly or intravenously daily for 10–14 days	Follow treatment with benzathine penicillin G 2.4 million units intramuscularly weekly for up to 3 weeks

¹Penicillin is the only documented effective treatment in pregnancy; pregnant patients with true allergy should be desensitized and treated with penicillin according to stage of disease as above.

²Patients treated with alternative therapies require close clinical and serologic monitoring.

³Fewer data for ceftriaxone treatment; optimal dose or duration not known.

CSF, cerebrospinal fluid

D. Public Health Measures

Counsel patients with infectious syphilis to abstain from sexual activity for 7–10 days after treatment. All cases of syphilis must be reported to the appropriate local public health agency in order to identify and treat sexual contacts. In addition, all patients with syphilis who are not known to be HIV-infected should have an HIV test at the time of diagnosis. Those with a negative HIV test should be offered HIV preexposure prophylaxis (HIV PrEP) because syphilis is associated with an increased risk of future HIV acquisition.

E. Treating Syphilis Contacts

Patients who have been sexually exposed to infectious syphilis within the preceding 3 months may be infected but seronegative and thus should be treated as for early syphilis even if serologic tests are negative. Persons exposed more than 3 months previously should be treated based on serologic results; however, if the patient is unreliable for follow-up, empiric therapy is indicated. Contacts of the persons with syphilis should be evaluated for HIV PrEP.

► Follow-Up Care

Because treatment failures and reinfection may occur, patients treated for syphilis should be monitored clinically and serologically with nontreponemal titers every 3–6 months. In primary and secondary syphilis, titers are expected to decrease fourfold by 12 months; however, titers from up to 20% of patients may fail to decrease. Optimal management of these patients is unclear, but at a minimum, close clinical and serologic follow-up is indicated. In HIV-negative patients, an HIV test should be repeated; a thorough neurologic history and examination should be performed and lumbar puncture considered since unrecognized neurosyphilis can be a cause of treatment failure. If symptoms or signs persist or recur after initial therapy or there is a four-fold or greater increase in nontreponemal titers, the patient has been reinfected (more likely) or the therapy failed (if a non-penicillin regimen was used). In those individuals, an HIV test should be performed, a lumbar puncture done (unless reinfection is a certainty), and re-treatment given as indicated above.

2. Secondary Syphilis



ESSENTIALS OF DIAGNOSIS

- Generalized maculopapular rash.
- Mucous membrane lesions.
- Condylomata lata in moist skin areas.
- Generalized nontender lymphadenopathy.
- Fever may be present.
- Meningitis, hepatitis, osteitis, arthritis, iritis.
- Many treponemes in moist lesions by immunofluorescence or darkfield microscopy.
- Positive serologic tests for syphilis.



▲ **Figure 34–2.** Papular squamous eruption of the hands and feet of a woman with secondary syphilis. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

► Clinical Findings

The secondary stage of syphilis usually appears a few weeks (or up to 6 months) after development of the chancre, when dissemination of *T pallidum* produces systemic signs (fever, lymphadenopathy) or infectious lesions at sites distant from the site of inoculation. The most common manifestations are skin and mucosal lesions. The skin lesions are nonpruritic, macular, papular, pustular, or follicular (or combinations of any of these types, but generally *not* vesicular) and generalized; involvement of the palms and soles (Figure 34–2) occurs in 80% of cases. Annular lesions simulating ringworm may be observed. Transillumination may help identify faint rashes, or rashes in persons with darker skin color. Mucous membrane lesions may include mucous patches (Figure 34–3), which can be found on the lips, mouth, throat, genitalia, and anus. Specific lesions—condylomata lata (Figure 34–4)—are fused, weeping papules on the moist skin areas and mucous membranes and are sometimes mistaken for genital warts. Unlike the dry rashes, the mucous membrane lesions are highly infectious.



▲ **Figure 34-3.** Secondary syphilis mucous patch of the tongue. (Used with permission from Kenneth Katz, MD, MSc, MSCE.)

Meningeal (aseptic meningitis or acute basilar meningitis), hepatic, renal, bone, and joint invasion may occur, with resulting cranial nerve palsies, jaundice, nephrotic syndrome, and periodontitis. Alopecia (moth-eaten appearance) and uveitis may also occur.

The serologic tests for syphilis are positive in almost all cases (see Primary Syphilis and Table 34-2). The moist cutaneous and mucous membrane lesions often show *T pallidum* on darkfield microscopic examination. A transient CSF lymphocytic pleocytosis (usually less than 50–100 cells/mcL [$0.05\text{--}0.1 \times 10^9/\text{L}$]) is seen in 40% of patients with secondary syphilis. There may be evidence of hepatitis or nephritis (immune complex type) as circulating immune complexes are deposited in blood vessel walls.

Skin lesions may be confused with the infectious exanthems, pityriasis rosea, and drug eruptions. Visceral lesions may suggest nephritis or hepatitis due to other causes.

► Treatment

Treatment is as for primary syphilis unless CNS or ocular disease or neurologic signs or symptoms are present, in which case a lumbar puncture should be performed. If examination of the fluid is positive (see Spinal fluid

examination for Neurosyphilis, below), treatment for neurosyphilis should be given (Table 34-3). See Primary Syphilis for follow-up care and treatment of contacts.

3. Latent Syphilis

ESSENTIALS OF DIAGNOSIS

- ▶ Early latent syphilis: infection < 1 year.
- ▶ Late latent syphilis: infection > 1 year.
- ▶ No physical signs.
- ▶ History of syphilis with inadequate treatment.
- ▶ Positive serologic tests for syphilis.

► General Considerations

Latent syphilis is the clinically quiescent phase in the absence of primary or secondary lesions; the diagnosis is made by positive serologic tests. **Early latent syphilis** is defined as the first year after primary infection and may relapse to secondary syphilis if undiagnosed or inadequately treated. Relapse is almost always accompanied by a rising titer in quantitative serologic tests; indeed, a rising titer may be the first or only evidence of relapse. About 90% of relapses occur during the first year after infection.

Early latent infection can be diagnosed if there was documented seroconversion or a fourfold increase in nontreponemal titers in the past 12 months; the patient can recall symptoms of primary or secondary syphilis; or the patient had a sex partner with documented primary, secondary, or early latent syphilis.

After the first year of latent syphilis, the patient is said to be in the **late latent stage** and noninfectious to sex partners. Transplacental transmission to a fetus, however, is possible in any phase. A diagnosis of late latent syphilis is justified only when the history and physical examination show no evidence of tertiary disease or neurosyphilis. The latent stage may last from months to a lifetime.

► Treatment

Treatment of early latent syphilis and follow-up are the same as for primary syphilis unless CNS disease is present (Table 34-3). Treatment of late latent syphilis is also shown in Table 34-3. The treatment of this stage of the disease is intended to prevent late sequelae. If there is evidence of CNS involvement, a lumbar puncture should be performed and, if positive, the patient should receive treatment for neurosyphilis (see Spinal fluid examination for Neurosyphilis, below). Titers may not decline as rapidly following treatment compared to early syphilis. Nontreponemal serologic tests should be repeated at 6, 12, and 24 months. If titers increase fourfold or if initially high titers (1:32 or higher) fail to decrease fourfold by 12–24 months or if symptoms or signs consistent with syphilis develop, an HIV test should be repeated in HIV-uninfected patients, lumbar puncture should be performed, and re-treatment given according to the stage of the disease.



▲ **Figure 34-4.** Secondary syphilis perianal condyloma lata. (Used with permission from Joseph Engelman, MD; San Francisco City Clinic.)

4. Tertiary (Late) Syphilis



ESSENTIALS OF DIAGNOSIS

- ▶ Infiltrative tumors of skin, bones, liver (gummas).
- ▶ Aortitis, aortic aneurysms, aortic regurgitation.
- ▶ CNS disorders: meningovascular and degenerative changes, paresthesias, shooting pains, abnormal reflexes, dementia, or psychosis.

► General Considerations

This stage may occur at any time after secondary syphilis, even after years of latency, and is rarely seen in developed countries in the modern antibiotic era. Late lesions are thought to represent an immunologic reaction to the organism and are usually divided into two types: (1) a localized hyperproliferative gummatous reaction with a relatively rapid onset and generally prompt response to therapy and (2) diffuse inflammation of a more insidious onset that characteristically involves the CNS and large arteries, may not improve despite treatment, and is often fatal if untreated. Gummas may involve any area or organ of the body but most often affect the skin or long bones. Cardiovascular disease is usually manifested by aortic aneurysm, aortic regurgitation, or aortitis. Various forms of diffuse or localized CNS involvement may occur.

Late syphilis must be differentiated from neoplasms of the skin, liver, lung, stomach, or brain; other forms of meningoencephalitis; and primary neurologic lesions.

Although almost any tissue and organ may be involved in late syphilis, the following are the most common types of involvement: skin, mucous membranes, skeletal system, eyes, respiratory system, gastrointestinal system, cardiovascular system, and nervous system.

► Clinical Findings

A. Symptoms and Signs

1. Skin—Cutaneous lesions of late syphilis are of two varieties: (1) multiple nodular lesions that eventually ulcerate (*lues maligna*) or resolve by forming atrophic, pigmented scars and (2) solitary gummas that start as painless subcutaneous nodules, then enlarge, attach to the overlying skin, and eventually ulcerate.

2. Mucous membranes—Late lesions of the mucous membranes are nodular gummas or leukoplakia, highly destructive to the involved tissue.

3. Skeletal system—Bone lesions are destructive, causing periostitis, osteitis, and arthritis with little or no associated redness or swelling but often marked myalgia and myositis of the neighboring muscles.

4. Eyes—Late ocular lesions are gummatous iritis, chorioretinitis, optic atrophy, and cranial nerve palsies, in addition to the lesions of CNS syphilis.

5. Respiratory system—Respiratory involvement is caused by gummatous infiltrates into the larynx, trachea, and

pulmonary parenchyma, producing discrete pulmonary densities. There may be hoarseness, respiratory distress, and wheezing secondary to the gummatous lesion itself or to subsequent stenosis occurring with healing.

6. Gastrointestinal system—Gummas involving the liver may be benign but can cause cirrhosis. Gastric involvement can consist of diffuse infiltration into the stomach wall or focal lesions that endoscopically and microscopically can be confused with lymphoma or carcinoma. Epigastric pain, early satiety, regurgitation, belching, and weight loss are common symptoms.

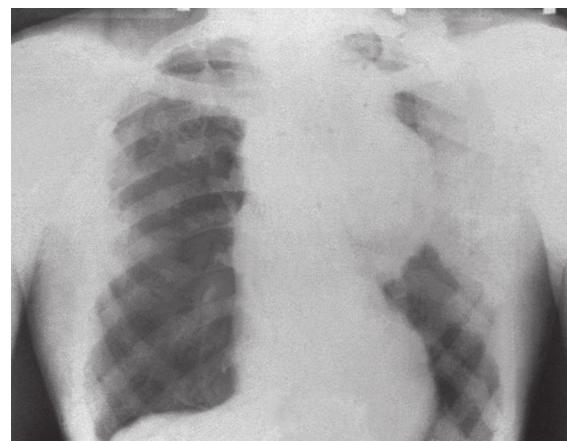
7. Cardiovascular system—Cardiovascular lesions (10–15% of tertiary syphilitic lesions) are often progressive, disabling, and life-threatening. CNS lesions are often present concomitantly. Involvement usually starts as an arteritis in the suprarenal portion of the aorta and progresses to one or more of the following: (1) narrowing of the coronary ostia, with resulting decreased coronary circulation, angina, and acute myocardial infarction; (2) scarring of the aortic valves, producing aortic regurgitation, and eventually heart failure; and (3) weakness of the wall of the aorta, with saccular aneurysm formation (Figure 34–5) and associated pressure symptoms of dysphagia, hoarseness, brassy cough, back pain (vertebral erosion), and occasionally rupture of the aneurysm. Recurrent respiratory infections are common as a result of pressure on the trachea and bronchi.

8. Nervous system (neurosyphilis)—See next section.

► Treatment

Treatment of tertiary syphilis (excluding neurosyphilis) is the same as late latent syphilis (Table 34–3); symptoms may not resolve after treatment. Positive serologic tests do not usually become negative.

The pretreatment clinical and laboratory evaluation should include neurologic, ocular, cardiovascular, psychiatric, and CSF examinations. In the presence of definite CSF or neurologic abnormalities, treat for neurosyphilis.



▲ **Figure 34–5.** Ascending saccular aneurysm of the thoracic aorta in tertiary syphilis. (Public Health Image Library, CDC.)

5. Neurosyphilis



ESSENTIALS OF DIAGNOSIS

- ▶ Can occur at any stage of disease.
- ▶ Consider both clinical presentation and laboratory data.
- ▶ Perform neurologic examination in all patients; consider CSF evaluation for atypical symptoms or lack of decrease in nontreponemal serology titers.

► General Considerations

Neurosyphilis can occur at any stage of disease and can be a progressive, disabling, and life-threatening complication. Asymptomatic CSF abnormalities and meningovascular syphilis occur earlier (months to years after infection, sometimes coexisting with primary and secondary syphilis) than tabes dorsalis and general paresis (2–50 years after infection).

► Clinical Findings

A. Classification

1. Asymptomatic neuroinvasion—This form has been reported in up to 40% of patients with early syphilis and is characterized by spinal fluid abnormalities (positive spinal fluid serology, lymphocytic pleocytosis, occasionally increased protein) without symptoms or signs of neurologic involvement. There are no clear data to support that these asymptomatic CSF abnormalities have clinical significance; therefore, unless treatment failure is suspected, routine CSF evaluation of asymptomatic patients is not recommended.

2. Meningovascular syphilis—This form is characterized by meningeal involvement or changes in the vascular structures of the brain (or both), producing symptoms of acute or chronic meningitis (headache, irritability); cranial nerve palsies (basilar meningitis); unequal reflexes; irregular pupils with poor light and accommodation reflexes; and when large vessels are involved, cerebrovascular accidents. The CSF shows lymphocytic pleocytosis ($100\text{--}1000/\text{mCL}$ [$0.1\text{--}1.0 \times 10^9/\text{L}$]) and elevated protein, and may have a positive serologic test (CSF VDRL) for syphilis. The symptoms of acute meningitis are rare in late syphilis.

3. Tabes dorsalis—This is a chronic progressive degeneration of the parenchyma of the posterior columns of the spinal cord and of the posterior sensory ganglia and nerve roots. The symptoms and signs are impairment of proprioception and vibration sense, Argyll Robertson pupils (which react poorly to light but accommodate for near focus), and muscular hypotonia and hyporeflexia. Impaired proprioception results in a wide-based gait and inability to walk in the dark. Paresthesias, analgesia, or sharp recurrent pains in the muscles of the leg (“shooting” or “lightning” pains) may occur. Joint damage may occur as a result of lack of sensory innervation (Charcot joint). The CSF may have a normal or increased lymphocytic cell count, elevated protein, and variable results of serologic tests.

4. General paresis—This is generalized involvement of the cerebral cortex with insidious onset of symptoms. There is usually a decrease in concentrating power, memory loss, dysarthria, tremor of the fingers and lips, irritability, and mild headaches. Most striking is the change of personality; the patient may become slovenly, irresponsible, confused, and psychotic. The CSF findings resemble those of tabes dorsalis. Combinations of the various forms of neurosyphilis (especially tabes and paresis) are not uncommon.

B. Laboratory Findings

See Serologic Tests for Syphilis, above; these tests should also be performed in cases of suspected neurosyphilis.

1. Indications for a lumbar puncture—In early syphilis (primary and secondary syphilis and early latent syphilis), invasion of the CNS by *T pallidum* with CSF abnormalities occurs commonly, but clinical neurosyphilis rarely develops in patients who have received standard therapy. Thus, unless clinical symptoms or signs of neurosyphilis or ocular involvement (uveitis, neuroretinitis, optic neuritis, iritis) are present, a lumbar puncture is not routinely recommended. CSF evaluation is recommended, however, if neurologic or ophthalmologic symptoms or signs are present, if there is evidence of treatment failure (see earlier discussion), or if there is evidence of active tertiary syphilis (eg, aortitis, iritis, optic atrophy, the presence of a gumma).

2. Spinal fluid examination—CSF findings in neurosyphilis are variable. In “classic” cases, there is an elevation of total protein above 46 mg/dL , lymphocytic pleocytosis of $5\text{--}100\text{ cells/mCL}$ ($0.005\text{--}0.1 \times 10^9/\text{L}$), and a positive CSF nontreponemal test. VDRL is more sensitive and preferred over RPR. The serum nontreponemal titers will be reactive in most cases. Because the CSF VDRL may be negative in 30–70% of cases of neurosyphilis, *a negative test does not exclude neurosyphilis*, while a positive test confirms the diagnosis. The CSF FTA-ABS is sometimes used; it is a highly sensitive test but lacks specificity, and a high serum titer of FTA-ABS may result in a positive CSF titer in the absence of neurosyphilis.

► Treatment

Neurosyphilis is treated with high doses of aqueous penicillin to achieve better penetration and higher drug levels in the CSF than is possible with benzathine penicillin G (Table 34-3). There are limited data for using ceftriaxone to treat neurosyphilis as well, but because other regimens have not been adequately studied, patients with a history of an IgE-mediated reaction to penicillin may require skin testing for allergy to penicillin and, if positive, should be desensitized. Because the 10- to 14-day treatment course for neurosyphilis is less than the 21 days recommended for treatment of late syphilis, CDC guidelines state that clinicians may consider giving an additional 2.4 million units of benzathine penicillin G intramuscularly once weekly for 1–3 weeks at the conclusion of the intravenous treatment.

All patients treated for neurosyphilis should have nontreponemal serologic tests done every 3–6 months. CDC guidelines recommend spinal fluid examinations at 6-month intervals until the CSF cell count is normal;

however, there are data to suggest that normalization of serum titers is an acceptable surrogate for CSF response. If the serum nontreponemal titers do not normalize, consider repeating the CSF analysis; expert consultation may be helpful in this scenario. A second course of penicillin therapy may be given if the CSF cell count has not decreased at 6 months or is not normal at 2 years.

6. Syphilis in HIV-Infected Patients

Syphilis is common among HIV-infected individuals. Some data suggest that syphilis coinfection is associated with an increase in HIV viral load and a decrease in CD4 count that normalizes with therapy; other studies have not found an association with HIV disease progression. Overall, for optimal patient care as well as prevention of transmission to partners, guidelines for the primary care of HIV-infected patients recommend at least annual syphilis screening.

Interpretation of serologic tests should be the same for HIV-positive and HIV-negative persons. If the diagnosis of syphilis is suggested on clinical grounds but nontreponemal antibody tests are negative, consider the prozone effect caused by very high titers (see Nontreponemal Antibody Tests, above), or try direct examination of primary or secondary lesions for spirochetes.

HIV-positive patients with primary and secondary syphilis should have careful clinical and serologic follow-up at 3-month intervals. The use of antiretroviral therapy has been associated with reduced serologic failure rates after syphilis treatment.

The diagnosis of neurosyphilis in HIV-infected patients is complicated by the fact that mild CSF abnormalities may be found in HIV infection alone. Evaluate patients for visual and hearing changes, since ocular and auditory syphilis may not result in CSF abnormalities. Like in HIV-uninfected patients, routine lumbar puncture is not recommended in asymptomatic patients; it should be reserved for cases in which neurologic symptoms or signs are present or there is concern for treatment failure. Following treatment, CSF white blood cell counts should normalize within 12 months regardless of HIV status, while the CSF VDRL may take longer. As discussed above, the same criteria for failure apply to HIV-positive and HIV-negative patients, and re-treatment regimens are the same.

For all stages and sites of syphilitic infection, treatment does not differ by HIV infection status.

7. Syphilis in Pregnancy

All pregnant women should have a nontreponemal serologic test for syphilis at the time of the first prenatal visit (see Chapter 19). In women who may be at increased risk for syphilis or for populations in which there is a high prevalence of syphilis, additional nontreponemal tests should be performed during the third trimester at 28 weeks and again at delivery. The serologic status of all women who have delivered should be known before discharge from the hospital. Seropositive women should be considered infected and should be treated unless prior treatment with fall in antibody titer is medically documented.

The only recommended treatment for syphilis in pregnancy is penicillin in dosage schedules appropriate for the stage of disease (Table 34–3). Penicillin prevents congenital syphilis in 90% of cases, even when treatment is given late in pregnancy. Women with a history of penicillin allergy should be skin tested and desensitized if necessary. *Tetracycline and doxycycline are contraindicated in pregnancy.*

The infant should be evaluated immediately at birth, and, depending on the likelihood of infection, monitored for clinical and serologic manifestations in the first year of life.

► Prevention of Syphilis

A randomized controlled trial of doxycycline postexposure prophylaxis for sexually transmitted infection prevention among men who have sex with men enrolled in a larger HIV PrEP study in France resulted in a 73% reduction in syphilis and 70% reduction in chlamydia. This strategy is not yet recommended, and further trials are underway to confirm the findings.

► When to Refer

- Consultation with the local public health department may help obtain all prior positive syphilis serologic results and may be helpful in complicated or atypical cases.
- Early (infectious) syphilis cases may be contacted for partner notification and treatment by local public health authorities.

► When to Admit

- Pregnant women with syphilis and true penicillin allergy should be admitted for desensitization and treatment.
- Women in late pregnancy treated for early syphilis should have close outpatient monitoring or be admitted because the Jarisch–Herxheimer reaction can induce premature labor.
- Patients with neurosyphilis usually require admission for treatment with aqueous penicillin.

Ghanem KG et al. The modern epidemic of syphilis. *N Engl J Med.* 2020;382:845. [PMID: 32101666]

Ropper AH. Neurosyphilis. *N Engl J Med.* 2019;381:1358. [PMID: 31577877]

Workowski KA et al; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64:1. [PMID: 26042815]

NON-SEXUALLY TRANSMITTED TREPONEMATOSES

A variety of treponemal diseases other than syphilis occur endemically in many tropical areas of the world. They are distinguished from disease caused by *T pallidum* by their nonsexual transmission via direct skin contact, their relatively high incidence in certain geographic areas and

among children, and their tendency to produce less severe visceral manifestations. As in syphilis, skin, soft tissue, and bone lesions may develop, organisms can be demonstrated in infectious lesions with darkfield microscopy or immunofluorescence, but cannot be cultured in artificial media; the serologic tests for syphilis are positive; molecular methods such as PCR and genome sequencing are available, but not widely used in endemic areas; the diseases have primary, secondary, and sometimes tertiary stages. Treatment with 2.4 million units of benzathine penicillin G intramuscularly is generally curative in any stage of the non-sexually transmitted treponematoses. In cases of penicillin hypersensitivity, tetracycline, 500 mg orally four times a day for 10–14 days, is usually the recommended alternative. In randomized controlled trials, oral azithromycin (30 mg/kg once) was noninferior to benzathine penicillin G for the treatment of yaws in children.

YAWS

Yaws, the most prevalent of the endemic treponematoses, is largely limited to tropical regions and is caused by *T pallidum* subspecies *pertenue*. It is characterized by granulomatous lesions of the skin, mucous membranes, and bone. Yaws is rarely fatal, though if untreated it may lead to chronic disability and disfigurement. Yaws is acquired by direct nonsexual contact, usually in childhood, although it may occur at any age. The “mother yaw,” a painless papule that later ulcerates, appears 3–4 weeks after exposure. There is usually associated regional lymphadenopathy. Six to 12 weeks later, secondary lesions occur, which are raised papillomas and papules that weep highly infectious material appear and last for several months or years. Painful ulcerated lesions on the soles are called “crab yaws” because of the resulting gait. Late gummatous lesions may occur, with associated tissue destruction involving large areas of skin and subcutaneous tissues. The late effects of yaws, with bone change, shortening of digits, and contractions, may be confused with similar changes occurring in leprosy. CNS, cardiac, or other visceral involvement is rare. See above for therapy. The World Health Organization has set a goal of eliminating yaws using mass treatment with azithromycin; however, emergence of macrolide resistance has complicated this approach.

Frimpong M et al. Multiplex recombinase polymerase amplification assay for simultaneous detection of *Treponema pallidum* and *Haemophilus ducreyi* in yaws-like lesions. *Trop Med Infect Dis*. 2020;5:157. [PMID: 33036234]

Marks M. Advances in the treatment of yaws. *Trop Med Infect Dis*. 2018;3:E92. [PMID: 30274488]

SELECTED SPIROCHETAL DISEASES

RELAPSING FEVER

The infectious organisms in relapsing fever are spirochetes of the genus *Borrelia*. The infection has two forms: tick-borne and louse-borne. The main reservoir for **tick-borne**

relapsing fever is rodents, which serve as the source of infection for ticks. Tick-borne relapsing fever may be transmitted transovarially from one generation of ticks to the next. Humans can be infected by tick bites or by rubbing crushed tick tissues or feces into the bite wound. Tick-borne relapsing fever is endemic, but is not transmitted from person to person. In the United States, infected ticks are found throughout the western states, but clinical cases are uncommon in humans.

The **louse-borne** form is primarily seen in the developing world, and humans are the only reservoir. Large epidemics may occur in louse-infested populations, and transmission is favored by crowding, malnutrition, and cold climate.

Clinical Findings

A. Symptoms and Signs

There is an abrupt onset of fever, chills, tachycardia, nausea and vomiting, arthralgia, and severe headache. Hepatomegaly and splenomegaly may develop, as well as various types of rashes (macular, papular, petechial) that usually occur at the end of a febrile episode. Delirium occurs with high fever, and there may be various neurologic and psychological abnormalities. The attack terminates, usually abruptly, after 3–10 days. After an interval of 1–2 weeks, relapse occurs, but often it is somewhat milder. Three to ten relapses may occur before recovery in tick-borne disease, whereas louse-borne disease is associated with only one or two relapses.

B. Laboratory Findings

During episodes of fever, large spirochetes are seen in thick and thin blood smears stained with Wright or Giemsa stain. The organisms can be cultured in special media but rapidly lose pathogenicity. The spirochetes can multiply in injected rats or mice and can be seen in their blood.

A variety of anti-*Borrelia* antibodies develop during the illness; sometimes the Weil–Felix test for rickettsioses and nontreponemal serologic tests for syphilis may also be falsely positive. Infection can cause false-positive indirect fluorescent antibody and Western blot tests for *Borrelia burgdorferi*, causing some cases to be misdiagnosed as Lyme disease. PCR assays can be performed on blood, CSF, and tissue but are not always available in endemic regions. CSF abnormalities occur in patients with meningeal involvement. Mild anemia and thrombocytopenia are common, but the white blood cell count tends to be normal.

Differential Diagnosis

The manifestations of relapsing fever may be confused with malaria, leptospirosis, meningococcemia, yellow fever, typhus, or rat-bite fever.

Prevention

Prevention of tick bites (as described for rickettsial diseases) and delousing procedures applicable to large groups can prevent illness. There are no vaccines for relapsing fever.

Postexposure prophylaxis with doxycycline 200 mg orally on day 1 and 100 mg daily for 4 days has been shown to prevent relapsing fever following tick bites in highly endemic areas.

► Treatment

A single dose of tetracycline or erythromycin, 0.5 g orally, or a single dose of procaine penicillin G, 600,000–800,000 units intramuscularly (adults), probably constitutes adequate treatment for louse-borne relapsing fevers; however, some experts advocate for longer courses of treatment to prevent persistent infection. In tick-borne disease, treatment begins with penicillin G, 3 million units intravenously every 4 hours, or ceftriaxone, 1 g intravenously daily; with clinical improvement, a 10-day course can be completed with 0.5 g of tetracycline or erythromycin given orally four times daily. If CNS invasion is suspected, intravenous penicillin G or ceftriaxone should be continued for 10–14 days. Jarisch–Herxheimer reactions occur commonly following treatment and may be life-threatening, so patients should be closely monitored (see Syphilis, above). All pregnant women with tick-borne disease should be treated for 14 days, ideally with intravenous penicillin or ceftriaxone.

► Prognosis

The overall mortality rate is usually about 5%. Fatalities are most common in older, debilitated, or very young patients. With treatment, the initial attack is shortened and relapses are largely prevented.

Talagrand-Reboul E. Relapsing fevers: neglected tick-borne diseases. *Front Cell Infect Microbiol*. 2018;8:98. [PMID: 29670860]
Warrell DA. Louse-borne relapsing fever (*Borrelia recurrentis* infection). *Epidemiol Infect*. 2019;147:e106. [PMID: 30869050]

RAT-BITE FEVER

Rat-bite fever is an uncommon acute infectious disease caused by the treponeme *Spirillum minus* (Asia) or the bacteria *Streptobacillus moniliformis* (North America). It is transmitted to humans by the bite of a rat. Inhabitants of rat-infested dwellings, owners of pet rats, and laboratory workers are at greatest risk.

► Clinical Findings

A. Symptoms and Signs

In *Spirillum* infections, the original rat bite, unless secondarily infected, heals promptly, but 1 to several weeks later, the site becomes swollen, indurated, and painful. It assumes a dusky purplish hue and may ulcerate. Regional lymphangitis and lymphadenitis, fever, chills, malaise, myalgia, arthralgia, and headache are present. Splenomegaly may occur. A sparse, dusky-red maculopapular rash appears on the trunk and extremities in many cases, and there may be frank arthritis.

After a few days, both the local and systemic symptoms subside, only to reappear several days later. This relapsing pattern of fever for 3–4 days alternating with afebrile

periods lasting 3–9 days may persist for weeks. The other features, however, usually recur only during the first few relapses. Endocarditis is a rare complication of infection.

B. Laboratory Findings

Leukocytosis is often present, and the nontreponemal test for syphilis is often falsely positive. The organism may be identified in darkfield examination of the ulcer exudate or aspirated lymph node material; more commonly, it is observed after inoculation of a laboratory animal with the patient's exudate or blood. It has not been cultured in artificial media.

► Differential Diagnosis

Rat-bite fever must be distinguished from the rat-bite-induced lymphadenitis and rash of streptobacillary fever. Clinically, the severe arthritis and myalgias seen in streptobacillary disease are rarely seen in disease caused by *S minus*. Reliable differentiation requires an increasing titer of agglutinins against *S moniliformis* or isolation of the causative organism. Other diseases in the differential include tularemia, rickettsial disease, *Pasteurella multocida* infections, and relapsing fever.

► Treatment

In acute illness, intravenous penicillin, 1–2 million units every 4–6 hours, is given initially; ceftriaxone 1 g intravenously daily is another option. Once improvement has occurred, therapy may be switched to oral penicillin V 500 mg four times daily, or amoxicillin 500 mg three times daily, to complete 10–14 days of therapy. For the penicillin-allergic patient, tetracycline 500 mg orally four times daily or doxycycline 100 mg twice a day can be used.

► Prognosis

The reported mortality rate of about 10% should be markedly reduced by prompt diagnosis and antimicrobial treatment.

Walker JW et al. Rat bite fever: a case report and review of the literature. *Pediatr Emerg Care*. 2019;35:e28. [PMID: 28002119]

LEPTOSPIROSIS

ESSENTIALS OF DIAGNOSIS

- Clinical illness can vary from asymptomatic to fatal liver and kidney failure.
- **Anicteric leptospirosis:** more common and milder form of the disease.
- **Icteric leptospirosis (Weil syndrome):** impaired kidney and liver function, abnormal mental status, and hemorrhagic pneumonia; 5–40% mortality rate.

► General Considerations

Leptospirosis is an acute and sometimes severe treponemal infection that is caused by several species within the genus *Leptospira*. The disease is distributed worldwide, and it is among the most common zoonotic infections. The leptospires enter through minor skin lesions and probably via the conjunctiva. Cases have occurred in international travelers after swimming or rafting in contaminated water, and occupational cases occur among sewer workers, rice planters, abattoir workers, and farmers. Sporadic urban cases have been seen in homeless persons exposed to rat urine.

► Clinical Findings

A. Symptoms and Signs

Anicteric leptospirosis, the more common and milder form of the disease, is often biphasic. After an incubation period of 2–20 days, the initial or “septicemic” phase begins with abrupt fever to 39–40°C, chills, abdominal pain, severe headache, and myalgias, especially of the calf muscles. There may be marked conjunctival suffusion. Leptospires can be isolated from blood, CSF, and tissues. Following a 1- to 3-day period of improvement in symptoms and absence of fever, the second or “immune” phase begins; however, in severe disease the phases may appear indistinct. Leptospires are absent from blood and CSF but are still present in the kidney, and specific antibodies appear. A recurrence of symptoms is seen as in the first phase of disease with the onset of meningitis. Uveitis, rash, nausea, vomiting, diarrhea, and adenopathy may occur. A rare but severe manifestation is hemorrhagic pneumonia. The illness is usually self-limited, lasting 4–30 days, and complete recovery is the rule.

Icteric leptospirosis (Weil syndrome) is the more severe form of the disease, characterized by impaired kidney and liver function, abnormal mental status, hemorrhagic pneumonia, hypotension, and a 5–40% mortality rate. Symptoms and signs often are continuous and not biphasic.

Leptospirosis with jaundice must be distinguished from hepatitis, yellow fever, rickettsial disease, and relapsing fever.

B. Laboratory Findings

The leukocyte count may be normal or as high as 50,000/mcL ($50 \times 10^9/L$), with neutrophils predominating. The urine may contain bile, protein, casts, and red cells. Oliguria is common, and in severe cases uremia may occur. Elevated bilirubin and aminotransferases are seen in 75%, and elevated creatinine (greater than 1.5 mg/dL) (132.6 mcmol/L) is seen in 50% of cases. Serum creatine kinase is usually elevated in persons with leptospirosis and normal in persons with hepatitis. In cases with meningeal involvement, organisms may be found in the CSF during the first 10 days of illness. Early in the disease, the organism may be identified by darkfield examination of the patient's blood (a test requiring expertise since false-positives are frequent in inexperienced hands) or by culture. Cultures take 1–6 weeks to become positive but may remain negative if antibiotics were started before culture was obtained. The organism

may also be grown from the urine from the tenth day to the sixth week. Diagnosis is usually made by means of serologic tests, including the microscopic agglutination test and enzyme-linked immunosorbent assay (ELISA). PCR molecular diagnostics are increasingly available and appear to be sensitive, specific, positive early in disease, and able to detect leptospiral DNA in blood, urine, CSF, and aqueous humor.

► Complications

Myocarditis, aseptic meningitis, acute kidney injury, and pulmonary infiltrates with hemorrhage are not common but are the usual causes of death. Iridocyclitis may occur.

► Prevention

The mainstay of prevention is avoidance of potentially contaminated food and water.

Prophylaxis with doxycycline (200 mg orally once a week) may be useful if a person is at high risk due to being in an area or season (eg, monsoon flooding) when exposure would be more likely. Human vaccine is used in some limited settings but is not widely available.

► Treatment

Many cases are self-limited without specific treatment. Many antibiotics, including penicillin, ceftriaxone, and tetracyclines, show antileptospiral activity; meta-analysis has not demonstrated a clear survival benefit for any antibiotic. Doxycycline (100 mg every 12 hours orally or intravenously), penicillin (eg, 1.5 million units every 6 hours intravenously), and ceftriaxone (1 g daily intravenously) are used in severe leptospirosis. Jarisch-Herxheimer reactions may occur (see Syphilis, above). Although therapy for mild disease is controversial, most clinicians treat with doxycycline, 100 mg orally twice daily, for 7 days, or amoxicillin, 50 mg/kg, divided into three doses daily. Azithromycin is also active, but clinical experience is limited.

► Prognosis

Without jaundice, the disease is almost never fatal. With jaundice, the mortality rate is 5% for those under age 30 years and 40% for those over age 60 years.

► When to Admit

Patients with jaundice or other evidence of severe disease should be admitted for close monitoring and may require admission to an intensive care unit.

Grennan D. JAMA patient page. Leptospirosis. JAMA. 2019; 321:812. [PMID: 30806697]

Jiménez JIS et al. Leptospirosis: report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care. 2018;43:361. [PMID: 29129539]

Karpagam KB et al. Leptospirosis: a neglected tropical zoonotic infection of public health importance—an updated review. Eur J Clin Microbiol Infect Dis. 2020;39:835. [PMID: 31898795]

LYME DISEASE (Lyme Borreliosis)



ESSENTIALS OF DIAGNOSIS

- ▶ Erythema migrans: a flat or slightly raised red lesion that expands with central clearing.
- ▶ Headache or stiff neck.
- ▶ Arthralgias, arthritis, and myalgias; arthritis is often chronic and recurrent.

► General Considerations

This illness, named after the town of Old Lyme, Connecticut, is the most common tick-borne disease in the United States and Europe and is caused by genospecies of the spirochete *B. burgdorferi*. Most US cases are reported from the mid-Atlantic, northeastern, and north central regions of the country. The true incidence of Lyme disease is not known for a number of reasons: (1) serologic tests are not standardized (see below); (2) clinical manifestations are nonspecific; and (3) even with reliable testing, serology is insensitive in early disease.

The tick vector of Lyme disease varies geographically and is *Ixodes scapularis* in the northeastern, north central, and mid-Atlantic regions of the United States; *Ixodes pacificus* on the West Coast; *Ixodes ricinus* in Europe; and *Ixodes persulcatus* in Asia. The disease also occurs in Australia. Mice and deer make up the major animal reservoir of *B. burgdorferi*, but other rodents and birds may also be infected. Domestic animals such as dogs, cattle, and horses can also develop clinical illness, usually manifested as arthritis.

Under experimental conditions, ticks must feed for 24–36 hours or longer to transmit infections. Most cases are reported in the spring and summer months. In addition, the percentage of ticks infected varies on a regional basis. In the northeastern and midwestern United States, 15–65% of *I. scapularis* ticks are infected with the spirochete; in the west, less than 5% of *I. pacificus* are infected. These are important epidemiologic features in assessing the likelihood that tick exposure will result in disease. Eliciting a history of brushing a tick off the skin (ie, the tick was not feeding) or removing a tick on the same day as exposure (ie, the tick did not feed long enough) decreases the likelihood that infection will develop.

Because the *Ixodes* tick is so small, the bite is usually painless and goes unnoticed. After feeding, the tick drops off in 2–4 days. If a tick is found, it should be removed immediately. The best way to accomplish this is to use fine-tipped tweezers to pull firmly and repeatedly on the tick's mouth part—not the tick's body—until the tick releases its hold. Saving the tick in a bottle of alcohol for future identification may be useful, especially if symptoms develop.

► Clinical Findings

The three stages of Lyme disease are classified based on early or late manifestations of the disease and whether it is localized or disseminated.

A. Symptoms and Signs

1. Stage 1, early localized infection—Stage 1 infection is characterized by erythema migrans (Figure 6–26). About 1 week after the tick bite (range, 3–30 days; median 7–10 days), a flat or slightly raised red lesion appears at the site, which is commonly seen in areas of tight clothing such as the groin, thigh, or axilla. This lesion expands over several days. Although originally described as a lesion that progresses with central clearing ("bulls-eye" lesion), often there is a more homogeneous appearance or even central intensification. About 10–20% of patients either do not have typical skin lesions or the lesions go unnoticed. Most patients with erythema migrans will have a concomitant viral-like illness (the "summer flu") characterized by myalgias, arthralgias, headache, and fatigue. Fever may or may not be present. Even without treatment, the symptoms and signs of erythema migrans resolve in 3–4 weeks. Although the classic lesion of erythema migrans is not difficult to recognize, atypical forms can occur that may lead to misdiagnosis. Southern tick-associated rash illness (STARI) has a similar appearance, but it occurs in geographically distinct areas of the United States.

Completely asymptomatic disease, without erythema migrans or flu-like symptoms, can occur but is very uncommon in the United States.

2. Stage 2, early disseminated infection—Up to 50–60% of patients with erythema migrans are bacteremic and within days to weeks of the original infection, secondary skin lesions develop in about 50% of patients. These lesions are similar in appearance to the primary lesion but are usually smaller. Malaise, fatigue, fever, headache (sometimes severe), neck pain, and generalized achiness are common with the skin lesions. Most symptoms are transient. After hematogenous spread, some patients experience cardiac (4–10% of patients) or neurologic (10–15% of patients) manifestations, including myopericarditis, with atrial or ventricular arrhythmias and heart block. Neurologic manifestations include both the central and peripheral nervous systems. The most common CNS manifestation is aseptic meningitis with mild headache and neck stiffness. The most common peripheral manifestation is a cranial nerve VII neuropathy, ie, facial palsy (usually unilateral but can be bilateral, see Figure 24–1). A sensory or motor radiculopathy and mononeuritis multiplex occur less frequently. Conjunctivitis, keratitis, and, rarely, panophthalmitis can also occur. Rarely, a cutaneous hypopigmented skin lesion called a borrelial lymphocytoma develops.

3. Stage 3, late persistent infection—Stage 3 infection occurs months to years after the initial infection and again primarily manifests itself as musculoskeletal, neurologic, and skin disease. In early reports, musculoskeletal complaints developed in up to 60% of patients, but with early recognition and treatment of disease, this has decreased to less than 10%. The classic manifestation of late disease is a monoarticular or oligoarticular arthritis most commonly affecting the knee or other large weight bearing joints. While these joints may be quite swollen, these patients generally report less pain compared to patients with bacterial septic arthritis. Even if untreated, the arthritis is

self-limited, resolving in a few weeks to months. Multiple recurrences are common but are usually less severe than the original disease. Joint fluid reflects an inflammatory arthritis with a mean white blood cell count of 25,000/mcL ($25 \times 10^9/L$) with a predominance of neutrophils. Chronic arthritis develops in about 10% of patients. The pathogenesis of chronic Lyme arthritis may be an immunologic phenomenon rather than persistence of infection.

Rarely, the nervous system (both central and peripheral) can be involved in late Lyme disease. In the United States, a subacute encephalopathy, characterized by memory loss, mood changes, and sleep disturbance, is seen. In Europe, a more severe encephalomyelitis caused by *B garinii* is seen and presents with cognitive dysfunction, spastic paraparesis, ataxia, and bladder dysfunction. Peripheral nervous system involvement includes intermittent paresthesias, often in a stocking glove distribution, or radicular pain.

The cutaneous manifestation of late infection, which can occur up to 10 years after infection, is acrodermatitis chronica atrophicans. It has been described mainly in Europe after infection with *B afzelii*. There is usually bluish-red discoloration of a distal extremity with associated swelling. These lesions become atrophic and sclerotic with time and eventually resemble localized scleroderma. Cases of diffuse fasciitis with eosinophilia, an entity that resembles scleroderma, have been rarely associated with infection with *B burgdorferi*.

B. Laboratory Findings

The diagnosis of Lyme disease is based on both clinical manifestations and laboratory findings. The US Surveillance Case Definition specifies a person with exposure to a potential tick habitat (within the 30 days just prior to developing erythema migrans) with (1) erythema migrans diagnosed by a clinician or (2) at least one late manifestation of the disease and (3) laboratory confirmation as fulfilling the criteria for Lyme disease.

Nonspecific laboratory abnormalities can occur, particularly in early disease. The most common are an elevated sedimentation rate of more than 20 mm/h seen in 50% of cases, and mildly abnormal liver biochemical tests are present in 30%. The abnormal liver biochemical tests are transient and return to normal within a few weeks of treatment. A mild anemia, leukocytosis (11,000–18,000/mcL) ($11\text{--}18 \times 10^9/L$), and microscopic hematuria have been reported in 10% or less of patients.

Laboratory confirmation requires serologic tests to detect specific antibodies to *B burgdorferi* in serum, preferably by ELISA and not by indirect immunofluorescence assay (IFA), which is less sensitive and specific and can cause misdiagnosis. A two-test approach is recommended for the diagnosis of active Lyme disease, with all specimens positive or equivocal by ELISA then confirmed with a Western immunoblot assay that can detect both IgM and IgG antibodies or with a different ELISA. A positive immunoblot requires that antibodies are detected against two (for IgM) or five (for IgG) specific protein antigens from *B burgdorferi*.

If a patient with suspected early Lyme disease has negative serologic studies, acute and convalescent titers should

be obtained since up to 50% of patients with early disease can be antibody negative in the first several weeks of illness. A fourfold rise in antibody titer would be diagnostic of recent infection. In patients with later stages of disease, almost all are antibody positive. False-positive reactions in the ELISA and IFA have been reported in juvenile rheumatoid arthritis, rheumatoid arthritis, systemic lupus erythematosus, infectious mononucleosis, subacute infective endocarditis, syphilis, relapsing fever, leptospirosis, enteroviral and other viral illnesses, and patients with gingival disease. False-negative serologic reactions occur early in illness, and antibiotic therapy early in disease can abort subsequent seroconversion.

The diagnosis of late nervous system Lyme disease is often difficult since clinical manifestations, such as subtle memory impairment, may be difficult to document. Most patients have a history of previous erythema migrans or monoarticular or polyarticular arthritis, and the vast majority have antibody present in serum. Patients with late disease and peripheral neuropathy almost always have positive serum antibody tests, usually have abnormal electrophysiology tests, and may have abnormal nerve biopsies showing perivascular collections of lymphocytes; however, the CSF is usually normal and does not demonstrate local antibody production.

Caution should be exercised in interpreting serologic tests because they are not subject to national standards, and inter-laboratory variation is a major problem. In addition, some laboratories perform tests that are entirely unreliable and should never be used to support the diagnosis of Lyme disease (eg, the Lyme urinary antigen test, immunofluorescent staining for cell wall-deficient forms of *B burgdorferi*, lymphocyte transformation tests, using PCR on inappropriate specimens such as blood or urine). Finally, testing is often done in patients with nonspecific symptoms such as headache, arthralgia, myalgia, fatigue, and palpitations. Even in endemic areas, the pretest probability of having Lyme disease is low, and the probability of a false-positive test result is greater than that of a true-positive result. For these reasons, the CDC has established guidelines for laboratory evaluation of patients with suspected Lyme disease:

1. The diagnosis of early Lyme disease is clinical (ie, exposure in an endemic area, with clinician-documented erythema migrans) and does *not* require laboratory confirmation. (Tests are often negative at this stage.)
2. Late disease requires objective evidence of clinical manifestations (recurrent brief attacks of monoarticular or oligoarticular arthritis of the large joints; lymphocytic meningitis, cranial neuritis [facial palsy], peripheral neuropathy or, rarely, encephalomyelitis—but *not* headache, fatigue, paresthesias, or stiff neck alone; atrioventricular conduction defects with or without myocarditis) and laboratory evidence of disease (two-stage testing with ELISA or IFA followed by Western blot, as described above).
3. Patients with nonspecific symptoms without objective signs of Lyme disease should *not* have serologic testing done. It is in this setting that false-positive tests occur more commonly than true-positive tests.

4. The role of serologic testing in nervous system Lyme disease is unclear, as sensitivity and specificity of CSF serologic tests have not been determined. However, it is rare for a patient to have positive serologic tests on CSF without positive tests on serum (see below).
5. Other tests such as the T cell proliferative assay and urinary antigen detection have not yet been studied well enough to be routinely used.

Cultures for *B burgdorferi* can be performed but are not routine and are usually reserved for clinical studies.

PCR is very specific for detecting the presence of *Borrelia* DNA, but sensitivity is variable and depends on which body fluid is tested, the stage of the disease, and collection and testing technique. In general, PCR is more sensitive than culture, especially in chronic disease but is not available in many clinical laboratories. Testing should not be done on blood or urine but has been successfully performed on synovial fluid and CSF. Up to 85% of synovial fluid samples are positive in active arthritis. In contrast, 38% of CSF samples in acute CNS Lyme disease are PCR positive compared with only 25% in chronic CNS disease. However, whether a positive PCR indicates persistence of viable organisms that will respond to further treatment or is only a marker for residual DNA (not active infection) has not been clarified. A negative PCR result does not rule out disease.

► Complications

B burgdorferi infection in pregnant women has not been associated with congenital syndromes, unlike other spirochetal illnesses such as syphilis.

Some patients and advocacy groups have claimed either a post-Lyme syndrome (in the presence of positive laboratory tests and after appropriate treatment) or “chronic Lyme disease” in which tests may all be negative. Both entities include nonspecific symptoms such as fatigue, myalgias, and cognitive difficulties (see Prognosis below). Expert groups are in agreement that there are no data to support that ongoing infection is the cause of either syndrome.

► Prevention

There is no human vaccine currently available. Simple preventive measures such as avoiding tick-infested areas, covering exposed skin with long-sleeved shirts and wearing long trousers tucked into socks, wearing light-colored clothing, using repellents, and inspecting for ticks after exposure will greatly reduce the number of tick bites. Environmental controls directed at limiting ticks on residential property would be helpful, but trying to limit the deer, tick, or white-footed mouse populations over large areas is not feasible.

Prophylactic antibiotic treatment following tick bites is recommended in certain high-risk situations if all of the following criteria are met: (1) a tick identified as an adult or nymphal *I scapularis* has been attached for at least 36 hours; (2) prophylaxis can be started within 72 hours of the time the tick was removed; (3) more than 20% of ticks

in the area are known to be infected with *B burgdorferi*; and (4) there is no contraindication to the use of doxycycline (not pregnant, age greater than 8 years, not allergic). The medication of choice for prophylaxis is a single 200-mg dose of doxycycline. If doxycycline is contraindicated, no prophylaxis should be given since short-course prophylactic therapy with other agents has not been studied. The patient should be closely monitored for early disease, and if early disease does develop, appropriate therapy is very effective in preventing long-term sequelae. Individuals who have removed ticks (including those who have had prophylaxis) should be monitored carefully for 30 days for possible coinfections.

► Coinfections

Lyme disease, babesiosis (see Chapter 35), and human granulocytic anaplasmosis (see Chapter 32) are endemic in similar areas of the country and are transmitted by the same tick, *I scapularis*. Coinfection with two or all three of these organisms can occur, causing a clinical picture that is not “classic” for any of these diseases. The presence of erythema migrans is highly suggestive of Lyme disease, whereas flu-like symptoms without rash are more suggestive of babesiosis or anaplasmosis. *Coinfection should be considered and excluded in patients who have persistent high fevers 48 hours after starting appropriate therapy for Lyme disease; in patients with persistent symptoms despite resolution of rash; and in those with anemia, leukopenia, or thrombocytopenia.*

► Treatment

Recommendations for therapy are outlined in Table 34–4. For erythema migrans, antibiotic therapy shortens the duration of rash and prevents late sequelae. Doxycycline is most commonly used and has the advantage of being active against anaplasmosis, a common coinfection. It has proven effective in shorter courses of 10–14 days compared to other regimens. Amoxicillin is also effective and is recommended for pregnant or lactating women and for those who cannot tolerate doxycycline. Cefuroxime axetil is as effective as doxycycline, but because of its cost, it should be considered an alternative choice for those who cannot tolerate doxycycline or amoxicillin or for those in whom the medications are contraindicated. Erythromycin and azithromycin are less effective, associated with higher rates of relapse, and are not recommended as first-line therapy.

Isolated facial palsy (without meningitis or peripheral neuropathy) can be treated with doxycycline, amoxicillin, or cefuroxime axetil for 2–3 weeks. Therapy does not affect the rate of resolution of the cranial neuropathy, but it does prevent development of late disease manifestations.

The need for a lumbar puncture in patients with seventh nerve palsy is controversial. Some clinicians perform lumbar puncture on all patients with facial palsy and others only if there are symptoms or signs of meningitis. If meningitis is present, parenteral therapy with ceftriaxone or penicillin is recommended in US guidelines. However, several European studies support doxycycline 400 mg/day orally for 14 days as equally effective.

Table 34–4. Treatment of Lyme disease.

Manifestations	Medication and Dosage
Tick bite	No treatment in most circumstances (see text); observe
Erythema migrans¹	Doxycycline, 100 mg orally twice daily for 10–14 days, or amoxicillin, 500 mg orally three times daily for 2–3 weeks, or cefuroxime axetil, 500 mg orally twice daily for 2–3 weeks
Neurologic disease	
Facial palsy (without meningitis)	Doxycycline, amoxicillin, or cefuroxime axetil as above for 2–3 weeks
Other central nervous system disease	Ceftriaxone, 2 g intravenously once daily, or penicillin G, 18–24 million units daily intravenously in six divided doses, or cefotaxime, 2 g intravenously every 8 hours—all for 2–4 weeks. Doxycycline, 100 mg orally twice daily for 2–4 weeks (not in US guidelines, but supported by trial data in Europe)
Cardiac disease	
Atrioventricular block and myopericarditis ²	An oral or parenteral (if more severe disease) regimen as described above can be used
Arthritis	
Oral dosage	Doxycycline, amoxicillin, or cefuroxime axetil as above for 28 days (see text)
Parenteral dosage	Ceftriaxone, cefotaxime, or penicillin G as above for 2–4 weeks
Acrodermatitis chronica atrophicans	Doxycycline, amoxicillin, or cefuroxime axetil as above for 3 weeks
“Chronic Lyme disease” or “post-Lyme disease syndrome”	Symptomatic therapy; prolonged antibiotics are <i>not</i> recommended

¹Patients who cannot tolerate tetracyclines or beta-lactams can be treated with azithromycin 500 mg orally daily for 10 days.

²Symptomatic patients, those with second- or third-degree block, and those with first-degree block with a PR interval \geq 300 milliseconds should be hospitalized for observation.

Patients with atrioventricular block or myopericarditis (or both) can be treated with either oral or parenteral agents for 2–3 weeks. Hospitalization and observation are indicated for symptomatic patients, those with second- or third-degree block, and those with first-degree block with a PR interval of 300 milliseconds or more. Once stabilized, hospitalized patients can be transitioned to one of the oral regimens to complete therapy.

Therapy of arthritis is difficult because some patients do not respond to any therapy, and those who do respond may do so slowly. Oral agents (doxycycline, amoxicillin, or cefuroxime axetil) are as effective as intravenous regimens (ceftriaxone, cefotaxime, or penicillin). A reasonable approach to the patient with Lyme arthritis is to start with oral therapy for 28 days. If there is partial resolution, re-treat with an additional 28 days of the same oral regimen. However, if there has been no response or worsening with initial oral therapy, switch to intravenous ceftriaxone for 14–28 days. If arthritis persists after re-treatment, symptomatic therapy with nonsteroidal anti-inflammatory drugs is recommended. For severe refractory pain, synovectomy may be required.

Based on limited data, therapy of Lyme disease in pregnancy should be the same as therapy in other patients with the exception that doxycycline should not be used.

Clinicians may encounter patients with nonspecific symptoms (such as fatigue and myalgias) and positive serologic tests for Lyme disease who request therapy for their illness. When treating these patients, clinicians must remember (1) that nonspecific symptoms alone are not diagnostic; (2) that serologic tests are fraught with

difficulty (as noted above), and in areas where disease prevalence is low, false-positive serologic tests are much more common than true-positive tests; and (3) that parenteral therapy with ceftriaxone for 2–4 weeks is costly and can cause significant adverse effects, including cholelithiasis and *Clostridioides difficile* colitis. Parenteral therapy should be reserved for those most likely to benefit, ie, those with characteristic cutaneous, neurologic, cardiac, or rheumatic manifestations of Lyme disease.

► Prognosis

Most patients respond to appropriate therapy with prompt resolution of symptoms within 4 weeks. True treatment failures are thus uncommon, and in most cases re-treatment or prolonged treatment of Lyme disease is instituted because of misdiagnosis or misinterpretation of serologic results (both IgG and IgM antibodies can persist for prolonged periods despite adequate therapy) rather than inadequate therapy or response. Prolonged courses of antibiotic therapy for nonspecific symptoms that persist after completion of appropriate assessment (and treatment, if necessary) for Lyme disease is not recommended.

The long-term outcome of adult patients with Lyme disease is generally favorable, but some patients have chronic complaints. Joint pain, memory impairment, and poor functional status because of pain are common subjective complaints, but physical examination and neurocognitive testing fail to document the presence of these symptoms as objective sequelae.

Immunity is not complete after Lyme disease. Reinfestation, although uncommon, is predominantly seen in patients successfully treated for early disease (erythema migrans) in whom antibody titers do not develop. Clinical manifestations and serologic response are similar to an initial infection.

► When to Refer

Consultation with an infectious diseases specialist with experience in diagnosing and treating Lyme disease can be helpful in atypical or prolonged cases.

► When to Admit

Admission for parenteral antibiotics is indicated for any patient with symptomatic CNS or cardiac disease as well as

those with second- or third-degree atrioventricular block, or first-degree block with a PR interval of 300 milliseconds or more.

Cardenas-de la Garza JA et al. Clinical spectrum of Lyme disease. *Eur J Clin Microbiol Infect Dis.* 2019;38:201. [PMID: 30456435]

Eldin C et al. Review of European and American guidelines for the diagnosis of Lyme borreliosis. *Med Mal Infect.* 2019; 49:121. [PMID: 30528068]

Kortela E et al. Oral doxycycline compared to intravenous ceftriaxone in the treatment of Lyme neuroborreliosis: a multicentre, equivalence, randomized, open-label trial. *Clin Infect Dis.* 2021;72:1323. [PMID: 32133487]

Protozoal & Helminthic Infections

Philip J. Rosenthal, MD

35

▼ PROTOZOAL INFECTIONS

AFRICAN TRYPANOSOMIASIS (Sleeping Sickness)



ESSENTIALS OF DIAGNOSIS

- ▶ Exposure to tsetse flies; chancre at bite site uncommon.
- ▶ **Hemolymphatic disease:** Irregular fever, headache, joint pain, rash, edema, lymphadenopathy.
- ▶ **Meningoencephalitic disease:** Somnolence, severe headache, progressing to coma.
- ▶ Trypanosomes in blood or lymph node aspirates; positive serologic tests.
- ▶ Trypanosomes and increased white cells and protein in cerebrospinal fluid.

► General Considerations

African trypanosomiasis is caused by the hemoflagellates *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*. The organisms are transmitted by bites of tsetse flies (genus *Glossina*), which inhabit shaded areas along streams and rivers. Trypanosomes ingested in a blood meal develop over 18–35 days in the fly; when the fly feeds again on a mammalian host, the infective stage is injected. Human disease occurs in rural areas of sub-Saharan Africa from south of the Sahara to about 30 degrees south latitude. *T b gambiense* causes West African trypanosomiasis and is transmitted in the moist sub-Saharan savannas and forests of west and central Africa. *T b rhodesiense* causes East African trypanosomiasis and is transmitted in the savannas of east and southeast Africa.

T b rhodesiense infection is primarily a zoonosis of game animals and cattle; humans are infected sporadically. Humans are the principal mammalian host for *T b gambiense*, but domestic animals can be infected. The number of reported cases increased from the 1960s to the 1990s and has since decreased greatly, although cases

are reported from over 20 countries. Total incidence has been estimated at less than 5000 cases per year, mostly due to *T b gambiense*, with the largest number in the Democratic Republic of the Congo. Infections are rare among travelers, including visitors to game parks.

► Clinical Findings

A. Symptoms and Signs

1. West African trypanosomiasis—Chancres at the site of the bite are uncommon. After an asymptomatic period that may last for months, hemolymphatic disease presents with fever, headache, myalgias, arthralgias, weight loss, and lymphadenopathy, with discrete, nontender, rubbery nodes, referred to as Winterbottom sign when in a posterior cervical distribution. Other common signs are mild splenomegaly, transient edema, and a pruritic erythematous rash. Febrile episodes may be broken by afebrile periods of up to several weeks. The hemolymphatic stage progresses over months to meningoencephalitic disease, with somnolence, irritability, personality changes, severe headache, and parkinsonian symptoms progressing to coma and death.

2. East African trypanosomiasis—Chancres at the bite site are more commonly recognized with *T b rhodesiense* infection, with a painful lesion of 3–10 cm and regional lymphadenopathy that appears about 48 hours after the tsetse fly bite and lasts 2–4 weeks. East African disease follows a much more acute course, with the onset of symptoms usually within a few days of the insect bite. The hemolymphatic stage includes intermittent fever and rash, but lymphadenopathy is less common than with West African disease. Myocarditis can cause tachycardia and death due to arrhythmias or heart failure. If untreated, East African trypanosomiasis progresses over weeks to months to meningoencephalitic disease, somnolence, coma, and death.

B. Laboratory Findings

Diagnosis can be difficult, and definitive diagnosis requires identification of trypanosomes. Microscopic examination of fluid expressed from a chancre or lymph node may show motile trypanosomes or, in fixed specimens, parasites

stained with Giemsa. During the hemolymphatic stage, detection of parasites in Giemsa-stained blood smears is common in East African disease but difficult in West African disease. Serial specimens should be examined, since parasitemias vary greatly over time. Meningoencephalitic (or second stage) disease is defined by the World Health Organization (WHO) as cerebrospinal fluid (CSF) showing at least five mononuclear cells per microliter, elevated protein, or presence of trypanosomes. Concentration techniques can aid identification of parasites in blood or CSF. Serologic tests are also available. The card agglutination test for trypanosomes (CATT) has excellent sensitivity and specificity for West African disease and can be performed in the field, but the diagnosis should be confirmed by identification of the parasites. Field-applicable immunochromatographic lateral flow rapid diagnostic tests that cost less than CATT and are simpler to perform are available; combining tests improves sensitivity and specificity. Molecular diagnostic tests, including PCR and field-friendly loop-mediated isothermal amplification (LAMP), are available, but these are not yet standardized or routinely available.

► Treatment

Detection of trypanosomes is a prerequisite for treatment of African trypanosomiasis because of the significant toxicity of most available therapies. Treatment recommendations depend on the type of trypanosomiasis (Table 35–1), which is determined by geography, and stage of disease, which requires examination of CSF. Eflornithine, nifurtimox, suramin, and melarsoprol are available in the United States from the CDC Drug Service (www.cdc.gov/laboratory/drugservice).

A. West African Trypanosomiasis

Pentamidine (4 mg/kg intramuscularly or intravenously every day or every other day for 7 days) has been used to treat infection that does not involve the central nervous system (CNS). The side effects of pentamidine include immediate hypotension; tachycardia; gastrointestinal

symptoms during administration; sterile abscesses; and pancreatic (hypoglycemia), liver, and kidney abnormalities. An alternate drug for early stage infection is eflornithine (100 mg/kg/day intravenously every 6 hours for 14 days).

The treatment of choice for CNS infection has been a combination of intravenous eflornithine (400 mg/kg/day in two doses for 7 days) and oral nifurtimox (15 mg/kg/day in three doses for 10 days), which has improved efficacy and less toxicity than older regimens. Eflornithine, though less toxic than older trypanocidal drugs, can cause gastrointestinal symptoms, bone marrow suppression, seizures, and alopecia. An alternative agent is melarsoprol. Fexinidazole is as effective and safe as eflornithine plus nifurtimox when administered orally over 10 days; this drug has been endorsed by the WHO for both early and CNS infection and will likely replace other therapies for all but advanced CNS disease. Fexinidazole is recommended for persons 6 years of age and older, with body weight at least 20 kg, and a CSF leukocyte count below 100/mcL ($0.1 \times 10^9/L$) (evaluation of CSF can be avoided if there is no suspicion of severe CNS disease). The drug has an acceptable safety profile, in particular compared to older therapies, but adverse events include headache, nausea, vomiting, insomnia, anxiety, weakness, tremor, and decreased appetite. For advanced CNS disease (CNS leukocytes more than 100/mcL [$0.1 \times 10^9/L$]), eflornithine plus nifurtimox is recommended.

B. East African Trypanosomiasis

Pentamidine and eflornithine are not reliably effective, and early disease is treated with suramin. The dosing regimens of suramin vary (eg, 100–200 mg test dose, then 20 mg/kg [maximum 1 g] intravenously on days 1, 3, 7, 14, and 21 or weekly for five doses). Suramin toxicities include vomiting and, rarely, seizures and shock during infusions as well as subsequent fever, rash, headache, neuropathy, and kidney and bone marrow dysfunction.

Suramin does not enter the CNS, so East African trypanosomiasis involving the CNS is treated with melarsoprol (three series of 3.6 mg/kg/day intravenously for 3 days, with 7-day breaks between the series or a 10-day intravenous course with 0.6 mg/kg on day 1, 1.2 mg/kg on day 2, and 1.8 mg/kg on days 3–10). Melarsoprol also acts against West African disease, but eflornithine plus nifurtimox is preferred due to its lower toxicity. Immediate side effects of melarsoprol include fever and gastrointestinal symptoms. The most important side effect is a reactive encephalopathy that can progress to seizures, coma, and death. To help avoid this side effect, corticosteroids are coadministered (dexamethasone 1 mg/kg/day intravenously for 2–3 days or oral prednisolone 1 mg/kg/day for 5 days, and then 0.5 mg/kg/day until treatment completion). In addition, increasing resistance to melarsoprol is a serious concern.

► Prevention & Control

Individual prevention in endemic areas should include neutral-colored clothes (eg, long sleeve shirts and pants), insect repellents, and mosquito nets. Control programs focusing on vector elimination and treatment of infected

Table 35–1. Treatment of African trypanosomiasis.

Disease	Stage	Treatment	
		First Line	Alternative
West African	Early	Fexinidazole	Pentamidine Suramin Eflornithine
	CNS involvement	Fexinidazole (< 100 leukocytes/mcL [$0.1 \times 10^9/L$] in CNS) Eflornithine + nifurtimox	Melarsoprol
East African	Early	Suramin	Pentamidine
	CNS involvement	Melarsoprol	

CNS, central nervous system.

persons and animals have shown good success in many areas but suffer from limited resources.

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AMERICAN TRYPANOSOMIASIS (Chagas Disease)



Acute stage

- ▶ Inflammatory lesion at inoculation site.
- ▶ Fever.
- ▶ Hepatosplenomegaly; lymphadenopathy.
- ▶ Myocarditis.
- ▶ Parasites in blood are diagnostic.

Chronic stage

- ▶ Heart failure, cardiac arrhythmias.
- ▶ Thromboembolism.
- ▶ Megaeosophagus; megacolon.
- ▶ Serologic tests are usually diagnostic.

General Considerations

Chagas disease is caused by *Trypanosoma cruzi*, a protozoan parasite found only in the Americas; it infects wild animals and, to a lesser extent, humans from southern South America to the southern United States. An estimated 6–8 million people are infected, mostly in rural areas, with the highest national prevalence in Bolivia, Argentina, Paraguay, Ecuador, El Salvador, and Guatemala. Control efforts in endemic countries have decreased disease incidence to about 30,000 new infections and 14,000 deaths per year. The disease is often acquired in childhood. In many countries in South America, Chagas disease is the most important cause of heart disease. The vector is endemic in the southern United States where some animals are infected and a few instances of local transmission have been reported.

T cruzi is transmitted by reduviid (triatomine) bugs infected by ingesting blood from animals or humans who have circulating trypanosomes. Multiplication occurs in the digestive tract of the bug and infective forms are eliminated in feces. Infection in humans occurs when the parasite penetrates the skin through the bite wound, mucous membranes, or the conjunctiva. Transmission can also occur by blood transfusion, organ or bone marrow transplantation, congenital transfer, or ingestion of food contaminated with vector feces. From the bloodstream, *T cruzi* invades many cell types but has a predilection for myocardium, smooth

muscle, and CNS glial cells. Multiplication causes cellular destruction, inflammation, and fibrosis, with progressive disease over decades.

Clinical Findings

A. Symptoms and Signs

As many as 70% of infected persons remain asymptomatic. The **acute stage** is seen principally in children and lasts 1–2 months. The earliest findings are at the site of inoculation either in the eye—Romaña sign (unilateral edema, conjunctivitis, and lymphadenopathy)—or in the skin—a chagoma (swelling with local lymphadenopathy). Subsequent findings include fever, malaise, headache, mild hepatosplenomegaly, and generalized lymphadenopathy. Acute myocarditis and meningoencephalitis are rare but can be fatal.

An asymptomatic **latent period (indeterminate phase)** may last for life, but symptomatic disease develops in 10–30% of infected individuals, commonly many years after infection.

Chronic Chagas disease generally manifests as abnormalities in cardiac and smooth muscle. Cardiac disease includes arrhythmias, heart failure, and embolic disease. Smooth muscle abnormalities lead to megaesophagus and megacolon, with dysphagia, regurgitation, aspiration, constipation, and abdominal pain. These findings can be complicated by superinfections. In immunosuppressed persons, including AIDS patients and transplant recipients, latent Chagas disease may reactivate; findings have included brain abscesses and meningoencephalitis.

B. Diagnostic Testing

The diagnosis is made by detecting parasites in persons with suggestive findings who have resided in an endemic area. With acute infection, evaluation of fresh blood or buffy coats may show motile trypanosomes, and fixed preparations may show Giemsa-stained parasites. Concentration methods increase diagnostic yields. Trypanosomes may be identified in lymph nodes, bone marrow, or pericardial or spinal fluid. Molecular tests are highly sensitive and can be used to detect parasites in organ transplant recipients or after accidental exposure. When initial tests are unrevealing, xenodiagnosis using laboratory vectors, laboratory culture, or animal inoculation may provide a diagnosis, but these methods are expensive and slow.

Chronic Chagas disease is usually diagnosed serologically. Many serologic assays, including rapid diagnostic tests, are available, but sensitivity and specificity are not ideal; confirmatory assays are advised after an initial positive test, as is standard for blood bank testing in South America. The diagnosis of chronic disease with PCR remains suboptimal.

Treatment

Treatment is inadequate because the two drugs used, benznidazole and nifurtimox, often cause severe side effects, must be used for long periods, and are ineffective against chronic infection. In acute and congenital infections, the drugs can reduce the duration and severity of infection, but

cure is achieved in only about 70% of patients. During the chronic phase of infection, although parasitemia may disappear in up to 70% of patients, treatment does not clearly alter the progression of the disease. In a 2015 trial for Chagas cardiomyopathy, benznidazole significantly reduced parasite detection but not progression of cardiac disease. Nevertheless, there is general consensus that treatment should be considered in all *T cruzi*-infected persons regardless of clinical status or time since infection. In particular, treatment is recommended for acute, congenital, and reactivated infections and for children and young adults with chronic disease. Both drugs are FDA-approved for the treatment of Chagas disease: benznidazole in children 2–12 years old and nifurtimox in children under 18 years of age and weighing at least 2.5 kg. Nifurtimox is available in the United States from the CDC Drug Service (www.cdc.gov/laboratory/drugservice).

Benznidazole is generally preferred due to better efficacy and safety profiles. It is given orally at a dosage of 5 mg/kg/day in two divided doses for 60 days. Its side effects include granulocytopenia, rash, and peripheral neuropathy. Nifurtimox is given orally in daily doses of 8–10 mg/kg in four divided doses after meals for 90–120 days. Side effects include gastrointestinal (anorexia, vomiting) and neurologic (headaches, ataxia, insomnia, seizures) symptoms, which appear to be reversible and to lessen with dosage reduction. For both drugs, some recommendations suggest higher dosing for acute infections. Patients with chronic Chagas disease may also benefit from antiarrhythmic therapy, standard therapy for heart failure, and conservative and surgical management of megaesophagus and megacolon.

► Prevention & Control

In South America, a major eradication program based on improved housing, use of residual pyrethroid insecticides and pyrethroid-impregnated bed curtains, and screening of blood donors has achieved striking reductions in new infections. In endemic areas and ideally in donors from endemic areas, blood should not be used for transfusion unless at least two serologic tests are negative.

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LEISHMANIASIS



ESSENTIALS OF DIAGNOSIS

- Sand fly bite in an endemic area.
- **Visceral leishmaniasis:** irregular fever, progressive hepatosplenomegaly, pancytopenia, wasting.
- **Cutaneous leishmaniasis:** chronic, painless, moist ulcers or dry nodules.

- **Mucocutaneous leishmaniasis:** destructive nasopharyngeal lesions.
- Amastigotes in macrophages in aspirates, touch preparations, or biopsies.
- Positive culture, serologic tests, PCR, or skin test.

► General Considerations

Leishmaniasis is a zoonosis transmitted by bites of sand flies of the genus *Lutzomyia* in the Americas and *Phlebotomus* elsewhere. When sand flies feed on an infected host, the parasitized cells are ingested with the blood meal. Leishmaniasis is caused by about 20 species of *Leishmania*; taxonomy is complex. Clinical syndromes are generally dictated by the infecting species, but some species can cause more than one syndrome.

The estimated annual incidence of disease has been decreasing, with current estimates of 600,000 to 1 million annual cases of cutaneous disease and 50,000–90,000 cases of visceral disease. Progress against visceral disease has been greatest on the Indian subcontinent.

Visceral leishmaniasis (kala azar) is caused mainly by *Leishmania donovani* in the Indian subcontinent and East Africa; *Leishmania infantum* in the Mediterranean, Middle East, China, parts of Asia, and Horn of Africa; and *Leishmania chagasi* in South and Central America. Other species may occasionally cause visceral disease. Over 90% of cases occur in seven countries: Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan. In each locale, the disease has particular clinical and epidemiologic features. The incubation period is usually 4–6 months (range: 10 days to 24 months). Without treatment, the fatality rate reaches 90%. Early diagnosis and treatment reduce mortality to 2–5%.

About 90% of cases of **cutaneous leishmaniasis** occur in Afghanistan, Pakistan, Syria, Saudi Arabia, Algeria, Iran, Brazil, and Peru. Old World cutaneous leishmaniasis is caused mainly by *Leishmania tropica*, *Leishmania major*, and *Leishmania aethiopica* in the Mediterranean, Middle East, Africa, Central Asia, and Indian subcontinent. New World cutaneous leishmaniasis is caused by *Leishmania mexicana*, *Leishmania amazonensis*, and the species listed below for mucocutaneous disease in Central and South America. Mucocutaneous leishmaniasis (espundia) occurs in lowland forest areas of the Americas and is caused by *Leishmania braziliensis*, *Leishmania panamensis*, and *Leishmania peruviana*.

► Clinical Findings

A. Symptoms and Signs

1. **Visceral leishmaniasis (kala azar)**—Most infections are subclinical, but a small number progress to full-blown disease. A local nonulcerating nodule at the site of the sand fly bite may precede systemic manifestations but usually is inapparent. The onset of illness may be acute, within 2 weeks of infection, or insidious. Symptoms and signs include fever, chills, sweats, weakness, anorexia, weight

loss, cough, and diarrhea. The spleen progressively becomes greatly enlarged, firm, and nontender. The liver is somewhat enlarged, and generalized lymphadenopathy may occur. Hyperpigmentation of skin can be seen, leading to the name kala azar ("black fever"). Other signs include skin lesions, petechiae, gingival bleeding, jaundice, edema, and ascites. As the disease progresses, severe wasting and malnutrition are seen; death eventually occurs, often due to secondary infections, within months to a few years. Post-kala azar dermal leishmaniasis may appear after apparent cure in the Indian subcontinent and Sudan. It may simulate leprosy, with hypopigmented macules or nodules developing on preexisting lesions. Viscerotropic leishmaniasis has been reported in small numbers of American military personnel in the Middle East, with mild systemic febrile illnesses after *L tropica* infections.

2. Old World and New World cutaneous leishmaniasis—

Cutaneous swellings appear 1 week to several months after sand fly bites and can be single or multiple. Characteristics of lesions and courses of disease vary depending on the leishmanial species and host immune response. Lesions begin as small papules and develop into nonulcerated dry plaques or large encrusted ulcers with well-demarcated raised and indurated margins (Figure 35–1). Satellite lesions may be present. The lesions are painless unless secondarily infected. Local lymph nodes may be enlarged. Systemic symptoms are uncommon, but fever, constitutional symptoms, and regional lymphadenopathy may be seen. For most species, healing occurs spontaneously in months to a few years, but scarring is common.

Leishmaniasis recidivans is a relapsing form of *L tropica* infection associated with hypersensitivity, in which the primary lesion heals centrally, but spreads laterally, with extensive scarring. Diffuse cutaneous leishmaniasis involves spread from a primary lesion, with local dissemination of nodules and a protracted course. Disseminated cutaneous leishmaniasis involves multiple nodular or ulcerated lesions, often with mucosal involvement.



▲ Figure 35–1. Skin ulcer due to cutaneous leishmaniasis. Note the classic morphologic characteristics of this wound with its erythematous, nodular interior, surrounded by a raised border. (From Dr. Mae Melvin, Public Health Image Library, CDC.)

3. Mucocutaneous leishmaniasis (espundia)—In Latin America, mucosal lesions develop in a small percentage of persons infected with *L braziliensis* and some other species, usually months to years after resolution of a cutaneous lesion. Nasal congestion is followed by ulceration of the nasal mucosa and septum, progressing to involvement of the mouth, lips, palate, pharynx, and larynx. Extensive destruction can occur, and secondary bacterial infection is common.

4. Infections in patients with AIDS—Leishmaniasis is an opportunistic infection in persons with AIDS. Visceral leishmaniasis can present late in the course of HIV infection, with fever, hepatosplenomegaly, and pancytopenia. The gastrointestinal tract, respiratory tract, and skin may also be involved.

B. Laboratory Findings

Identifying amastigotes within macrophages in tissue samples provides a definitive diagnosis. In **visceral leishmaniasis**, fine-needle aspiration of the spleen for culture and tissue evaluation is generally safe, and yields a diagnosis in over 95% of cases. Bone marrow aspiration is less sensitive but safer and diagnostic in most cases, and Giemsa-stained buffy coat of peripheral blood may occasionally show organisms. Cultures with media available from the CDC will grow promastigotes within a few days to weeks. Molecular assays can also be diagnostic. Serologic tests may facilitate diagnosis, but none are sufficiently sensitive or specific to be used alone. Numerous antibody-based rapid diagnostic tests are available; these have shown good specificity but limitations in sensitivity outside of India. Antigen-based rapid diagnostic tests may offer improved sensitivity. For **cutaneous leishmaniasis**, biopsies should be taken from the raised border of a skin lesion, with samples for histopathology, touch preparation, and culture. The histopathology shows inflammation with mononuclear cells. Macrophages filled with amastigotes may be present, especially early in infection. An intradermal leishmanin (Montenegro) skin test is positive in most individuals with cutaneous disease but negative in those with progressive visceral or diffuse cutaneous disease; this test is not approved in the United States. In **mucocutaneous leishmaniasis**, diagnosis is established by detecting amastigotes in scrapings, biopsy preparations, or aspirated tissue fluid, but organisms may be rare. Cultures from these samples may grow organisms. Serologic studies are often negative, but the leishmanin skin test is usually positive.

► Treatment

A. Visceral Leishmaniasis

The treatment of choice for visceral leishmaniasis on the Indian subcontinent is liposomal amphotericin B (approved by the FDA), which is generally effective and well tolerated but expensive. Standard dosing is 3 mg/kg/day intravenously on days 1–5, 14, and 21. Simpler regimens that have shown good efficacy in India include four doses of 5 mg/kg over 4–10 days and a single dose of 15 mg/kg, but efficacies of shorter regimens have been lower outside India. A single infusion of an amphotericin B lipid emulsion, which is more affordable than liposomal preparations, showed

excellent efficacy, albeit lower than that of the liposomal formulation. Conventional amphotericin B deoxycholate, which is much less expensive, is also highly effective but with more toxicity. It is administered as a slow intravenous infusion of 1 mg/kg/day for 15–20 days or 0.5–1 mg/kg every second day for up to 8 weeks. Infusion-related side effects with conventional or liposomal amphotericin B include gastrointestinal symptoms, fever, chills, dyspnea, hypotension, and hepatic and renal toxicity.

Pentavalent antimonials remain the most commonly used drugs to treat leishmaniasis in most areas. Response rates are good outside India, but in India, resistance is a major problem. Two preparations are available, sodium stibogluconate in the United States and many other areas and meglumine antimonate in Latin America and franco-phone countries; the compounds appear to have comparable activities. In the United States, sodium stibogluconate can be obtained from the CDC Drug Service (www.cdc.gov/laboratory/drugservice). Standard dosing for either antimonial is 20 mg/kg once daily intravenously (preferred) or intramuscularly for 20 days for cutaneous leishmaniasis and 28 days for visceral or mucocutaneous disease. Toxicity increases over time, with development of gastrointestinal symptoms, fever, headache, myalgias, arthralgias, pancreatitis, and rash. Intramuscular injections can cause sterile abscesses. Monitoring should include serial ECGs, and changes are indications for discontinuation to avoid progression to serious arrhythmias.

The efficacy of amphotericin B is lower in East Africa than in Asia, and the standard treatment is a combination of sodium stibogluconate (20 mg/kg/day intravenously) plus paromomycin (15 mg/kg/day intramuscularly) for 17 days, with demonstrated excellent efficacy; liposomal amphotericin B may be considered in elderly or pregnant patients due to toxicity concerns.

Miltefosine is the first oral drug for the treatment of leishmaniasis, and it is registered in India for this indication. It initially demonstrated excellent results in India, but efficacy is decreasing due to drug resistance. It can be administered at a daily oral dose of 2.5 mg/kg in two divided doses for 28 days. A 14-day course plus a single dose of liposomal amphotericin B showed excellent efficacy. A 28-day course of miltefosine (2.5 mg/kg/day) is also effective for the treatment of New World cutaneous leishmaniasis. Vomiting, diarrhea, and elevations in transaminases and kidney function studies are common, but generally short-lived, side effects.

The aminoglycoside paromomycin (11 mg/kg/day intramuscularly for 21 days) was shown to be similarly efficacious to amphotericin B for the treatment of visceral disease in India, where it is approved for this indication. It is much less expensive than liposomal amphotericin B or miltefosine. The drug is well tolerated; side effects include ototoxicity and reversible elevations in liver enzymes.

The use of drug combinations to improve treatment efficacy, shorten treatment courses, and reduce the selection of resistant parasites has been actively studied. In India, compared to a standard 30-day (treatment on alternate days) course of amphotericin, noninferior efficacy and decreased adverse events were seen with a single dose of liposomal

amphotericin plus a 7-day course of miltefosine, a single dose of liposomal amphotericin plus a 10-day course of paromomycin, or a 10-day course of miltefosine plus paromomycin. A combination of sodium stibogluconate and paromomycin is the standard treatment in East Africa.

B. Cutaneous Leishmaniasis

In the Old World, cutaneous leishmaniasis is generally self-healing over some months and does not metastasize to the mucosa, so it may be justified to withhold treatment in regions without mucocutaneous disease if lesions are small and cosmetically unimportant. Lesions on the face or hands are generally treated. New World leishmaniasis has a greater risk of progression to mucocutaneous disease, so treatment is more often warranted. Standard therapy is with pentavalent antimonials for 20 days, as described above. Other treatments include those discussed above for visceral disease, azole antifungals, and allopurinol. In studies in South America, a 28-day course of miltefosine was superior to a 20-day course of meglumine antimonate, and oral fluconazole also showed good efficacy. Topical therapy has included intralesional antimony, intralesional pentamidine, paromomycin ointment, cryotherapy, local heat, and surgical removal. Diffuse cutaneous leishmaniasis and related chronic skin processes generally respond poorly to therapy.

C. Mucocutaneous Leishmaniasis

Cutaneous infections from regions where parasites include those that cause mucocutaneous disease (eg, *L brasiliensis* in parts of Latin America) should all be treated to help prevent disease progression. Treatment of mucocutaneous disease with antimonials is disappointing, with responses in only about 60% in Brazil. Other therapies listed above for visceral leishmaniasis may also be used, although they have not been well studied for this indication.

► Prevention & Control

Personal protection measures for avoidance of sand fly bites include use of insect repellants, fine-mesh insect netting, long sleeves and pants, and avoidance of warm shaded areas where flies are common. Disease control measures include destruction of animal reservoir hosts, mass treatment of humans in disease-prevalent areas, residual insecticide spraying in dwellings, limiting contact with dogs and other domesticated animals, and use of permethrin-impregnated collars for dogs.

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MALARIA



ESSENTIALS OF DIAGNOSIS

- ▶ Exposure to anopheline mosquitoes in a malaria-endemic area.
- ▶ Intermittent attacks of chills, fever, and sweating.
- ▶ Headache, myalgia, vomiting, splenomegaly; anemia, thrombocytopenia.
- ▶ Intraerythrocytic parasites identified in thick or thin blood smears or positive rapid diagnostic tests.
- ▶ **Falciparum malaria complications:** cerebral malaria, severe anemia, hypotension, pulmonary edema, acute kidney injury, hypoglycemia, acidosis, and hemolysis.

► General Considerations

Malaria is the most important parasitic disease of humans, causing hundreds of millions of illnesses and hundreds of thousands of deaths each year. The disease is endemic in most of the tropics, including much of South and Central America, Africa, the Middle East, the Indian subcontinent, Southeast Asia, and Oceania. Transmission, morbidity, and mortality are greatest in Africa, where most deaths from malaria are in young children. Malaria is also common in travelers from nonendemic areas to the tropics. Although the disease remains a major problem, impressive advances have been made in many regions. A 2016 study estimated a 57% decrease in the malaria death rate and 37% decrease in the annual number of malaria deaths in the past 15 years. However, after marked gains, morbidity and mortality appear to have leveled, with WHO estimates showing modest annual increases in incidence, but decreases in deaths (228 million cases and 405,000 deaths estimated in 2018); other estimates suggest greater morbidity and mortality.

Four species of the genus *Plasmodium* classically cause human malaria. *Plasmodium falciparum* is responsible for nearly all severe disease, since it uniquely infects erythrocytes of all ages and mediates the sequestration of infected erythrocytes in small blood vessels, thereby evading clearance by the spleen. *P. falciparum* is endemic in most malarious areas and is by far the predominant species in Africa. *Plasmodium vivax* is about as common as *P. falciparum* outside of Africa. *P. vivax* uncommonly causes severe disease, although this outcome may be more common than previously appreciated. *Plasmodium ovale* and *Plasmodium malariae* are much less common causes of disease, and generally do not cause severe illness. *Plasmodium knowlesi*, a parasite of macaque monkeys, causes illnesses in humans, including some severe disease, in Southeast Asia.

Malaria is transmitted by the bite of infected female anopheline mosquitoes. During feeding, mosquitoes inject sporozoites, which circulate to the liver, and rapidly infect hepatocytes, causing asymptomatic liver infection. Merozoites are subsequently released from the liver, and they rapidly infect erythrocytes to begin the asexual erythrocytic

stage of infection that is responsible for human disease. Multiple rounds of erythrocytic development, with production of merozoites that invade additional erythrocytes, lead to large numbers of circulating parasites and clinical illness. Some erythrocytic parasites also develop into sexual gametocytes, which are infectious to mosquitoes, allowing completion of the life cycle and infection of others.

Malaria may uncommonly be transmitted from mother to infant (congenital malaria), by blood transfusion, and in nonendemic areas by mosquitoes infected after biting infected immigrants or travelers. In *P. vivax* and *P. ovale*, parasites also form dormant liver hypnozoites, which are not killed by most drugs, allowing subsequent relapses of illness after initial elimination of erythrocytic infections. For all plasmodial species, parasites may recrudesce following initial clinical improvement after suboptimal therapy.

In highly endemic regions, where people are infected repeatedly, antimalarial immunity prevents severe disease in most older children and adults. However, young children, who are relatively nonimmune, are at high risk for severe disease from *P. falciparum* infection, and this population is responsible for most deaths from malaria. Pregnant women are also at increased risk for severe falciparum malaria. In areas with lower endemicity, individuals of all ages commonly present with uncomplicated or severe malaria. Travelers, who are generally nonimmune, are at high risk for severe disease from falciparum malaria at any age.

► Clinical Findings

A. Symptoms and Signs

An acute attack of malaria typically begins with a prodrome of headache and fatigue, followed by fever. A classic malarial paroxysm includes chills, high fever, and then sweats. Patients may appear to be remarkably well between febrile episodes. Fevers are usually irregular, especially early in the illness, but without therapy may become regular, with 48-hour (*P. vivax* and *P. ovale*) or 72-hour (*P. malariae*) cycles, especially with non-falciparum disease. Headache, malaise, myalgias, arthralgias, cough, chest pain, abdominal pain, anorexia, nausea, vomiting, and diarrhea are common. Seizures may represent simple febrile convulsions or evidence of severe neurologic disease. Physical findings may be absent or include signs of anemia, jaundice, splenomegaly, and mild hepatomegaly. Rash and lymphadenopathy are not typical in malaria, and thus suggestive of another cause of fever.

In the developed world, it is imperative that all persons with suggestive symptoms, in particular fever, who have traveled in an endemic area be evaluated for malaria. The risk for falciparum malaria is greatest within 2 months of return from travel; other species may cause disease many months—and occasionally more than a year—after return from an endemic area.

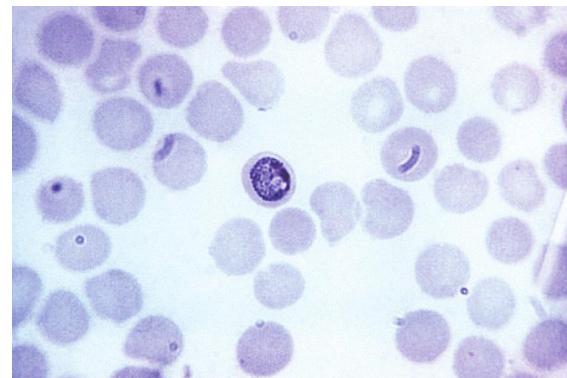
Severe malaria is principally a result of *P. falciparum* infection. It is characterized by signs of severe illness, organ dysfunction, or a high parasite load (peripheral parasitemia greater than 5% or greater than 200,000 parasites/mCL). Severe falciparum malaria can include dysfunction of any organ system, including neurologic abnormalities

progressing to alterations in consciousness, repeated seizures, and coma (cerebral malaria); severe anemia; hypotension and shock; noncardiogenic pulmonary edema and acute respiratory distress syndrome; acute kidney injury due to acute tubular necrosis or, less commonly, severe hemolysis; hypoglycemia; acidosis; hemolysis with jaundice; hepatic dysfunction; retinal hemorrhages and other fundoscopic abnormalities; bleeding abnormalities, including disseminated intravascular coagulation; and secondary bacterial infections, including pneumonia and *Salmonella* bacteremia. In the developing world, severe malaria and deaths from the disease are mostly in young children, in particular from cerebral malaria and severe anemia. Cerebral malaria is a consequence of a single severe infection while severe anemia follows multiple malarial infections, intestinal helminths, and nutritional deficiencies. In a large trial of African children, acidosis, impaired consciousness, convulsions, renal impairment, and underlying chronic illness were associated with poor outcome.

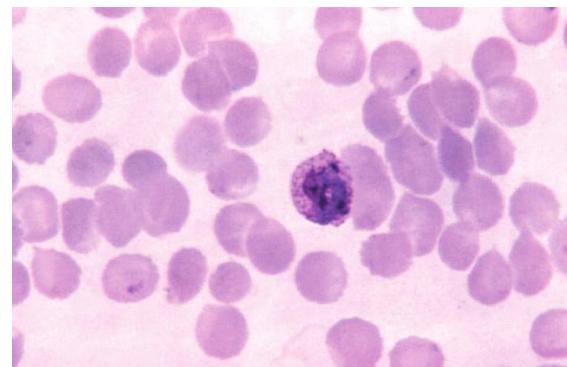
Uncommon disorders resulting from immunologic responses to chronic infection are massive splenomegaly and, with *P. malariae* infection, immune complex glomerulopathy with nephrotic syndrome. HIV-infected individuals are at increased risk for malaria and for severe disease, in particular with advanced immunodeficiency.

B. Laboratory Findings

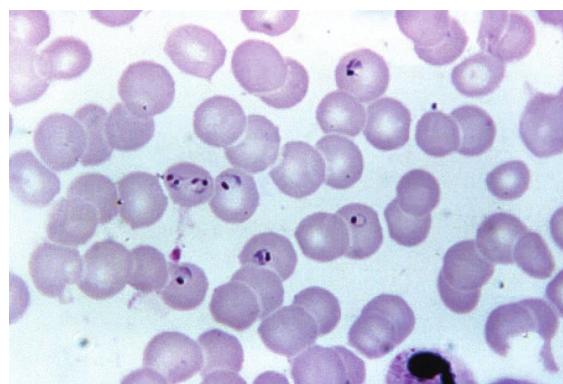
Giems-stained blood smears remain the mainstay of diagnosis (Figures 35–2, 35–3, 35–4, and 35–5), although other routine stains (eg, Wright stain) will also demonstrate parasites. Thick smears provide efficient evaluation of large volumes of blood, but thin smears are simpler for inexperienced personnel and better for discrimination of parasite species. Single smears are usually positive in infected individuals, although parasitemias may be very low in nonimmune individuals. If illness is suspected, repeating smears at 8- to 24-hour intervals is appropriate. The severity of malaria correlates only loosely with the quantity of infecting parasites, but high parasitemias (especially greater than 10–20% of erythrocytes infected or



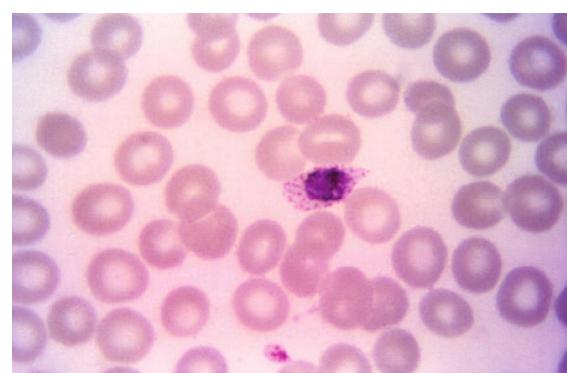
▲ **Figure 35–3.** Thin film Giemsa-stained micrograph with *Plasmodium malariae* trophozoite. (From Steven Glenn, Laboratory & Consultation Division, Public Health Image Library, CDC.)



▲ **Figure 35–4.** Thin film Giemsa-stained micrograph with *Plasmodium vivax* schizont. (From Steven Glenn, Laboratory & Consultation Division, Public Health Image Library, CDC.)



▲ **Figure 35–2.** Thin film Giemsa-stained micrograph with *Plasmodium falciparum* ring forms. (From Steven Glenn, Laboratory & Consultation Division, Public Health Image Library, CDC.)



▲ **Figure 35–5.** Thin film Giemsa-stained micrograph with *Plasmodium ovale* trophozoite. (From Steven Glenn, Laboratory & Consultation Division, Public Health Image Library, CDC.)

greater than 200,000–500,000 parasites/mcL) or the presence of malarial pigment (a breakdown product of hemoglobin) in more than 5% of neutrophils is associated with a particularly poor prognosis.

A second means of diagnosis is rapid diagnostic tests to identify circulating plasmodial antigens with a simple “dipstick” format. These tests are not well standardized but are widely available. At best, they offer sensitivity and specificity near that of high-quality blood smear analysis and are simpler to perform. However, *P falciparum* lacking the most common rapid diagnostic test antigen, histidine-rich protein 2 (HRP2), has been identified in some areas, leading to concern that HRP2-based tests may miss some cases of falciparum malaria.

Serologic tests indicate history of disease but are not useful for diagnosis of acute infection. PCR and related molecular tests (eg, LAMP) are highly sensitive but not available for routine diagnosis. In immune populations, highly sensitive molecular tests, such as PCR, have limited value because subclinical infections, which are not routinely treated, are common.

Other diagnostic findings with uncomplicated malaria include thrombocytopenia, anemia, leukocytosis or leukopenia, liver function abnormalities, and hepatosplenomegaly. Severe malaria can present with the laboratory abnormalities expected for the advanced organ dysfunction discussed above.

Treatment

Malaria is the most common cause of fever in much of the tropics and in travelers seeking medical attention after return from endemic areas. Fevers are often treated presumptively in endemic areas, but ideally, treatment should follow definitive diagnosis, especially in non-immune individuals.

Symptomatic malaria is caused only by the erythrocytic stage of infection. Available antimalarial drugs (Table 35–2) act against this stage, except for primaquine, which acts principally against hepatic parasites.

A. Non-Falciparum Malaria

The first-line drug for non-falciparum malaria from most areas remains chloroquine. Due to increasing resistance of *P vivax* to chloroquine, alternative therapies are recommended when resistance is suspected, particularly for infections acquired in Indonesia, Oceania, and South America. These infections can be treated with artemisinin-based combination therapies (ACTs) or other first-line regimens for *P falciparum* infections as discussed below. For *P vivax* or *P ovale*, eradication of erythrocytic parasites with chloroquine should be accompanied by treatment with primaquine or tafenoquine (after evaluating for glucose-6-phosphate dehydrogenase [G6PD] deficiency; see below) to eradicate dormant liver stages (hypnozoites),

Table 35–2. Major antimalarial drugs.

Drug	Class	Use
Chloroquine	4-Aminoquinoline	Treatment and chemoprophylaxis of infection with sensitive parasites
Amodiaquine ¹	4-Aminoquinoline	Treatment of <i>Plasmodium falciparum</i> , optimally in fixed combination with artesunate
Piperaquine ¹	4-Aminoquinoline	Treatment of <i>P falciparum</i> in fixed combination with dihydroartemisinin
Quinine	Quinoline methanol	Oral and intravenous ¹ (for severe infections) treatment of <i>P falciparum</i>
Quinidine	Quinoline methanol	Intravenous therapy of severe infections with <i>P falciparum</i>
Mefloquine	Quinoline methanol	Chemoprophylaxis and treatment of infections with <i>P falciparum</i>
Primaquine, tafenoquine	8-Aminoquinoline	Radical cure and terminal prophylaxis of infections with <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> ; alternative for malaria chemoprophylaxis
Sulfadoxine-pyrimethamine (Fansidar)	Folate antagonist combination	Treatment of <i>P falciparum</i> , optimally in combination with artesunate; intermittent preventive therapy
Atovaquone-proguanil (Malarone)	Quinone-folate antagonist combination	Treatment and chemoprophylaxis of <i>P falciparum</i> infection
Doxycycline	Tetracycline	Treatment (with quinine) of infections with <i>P falciparum</i> ; chemoprophylaxis
Halofantrine ¹	Phenanthrene methanol	Treatment of infections with some chloroquine-resistant <i>P falciparum</i>
Lumefantrine	Amyl alcohol	Treatment of <i>P falciparum</i> malaria in fixed combination with artemether (Coartem)
Pyronaridine	Benzonaphthyridine	Treatment of <i>P falciparum</i> malaria in fixed combination artesunate
Artemisinins (artesunate, artemether, dihydroartemisinin)	Sesquiterpene lactone endoperoxides	Treatment of <i>P falciparum</i> in oral combination regimens for uncomplicated disease and parenterally for severe malaria

¹Not available in the United States.

Modified, with permission, from Katzung BG. *Basic & Clinical Pharmacology*, 14th edition. McGraw-Hill, 2018.

which may lead to relapses with recurrent erythrocytic infection and malaria symptoms after weeks to months if left untreated. *P. malariae* infections need only be treated with chloroquine.

B. Uncomplicated Falciparum Malaria

P. falciparum is resistant to chloroquine and sulfadoxine-pyrimethamine in most areas, with the exceptions of Central America west of the Panama Canal and Hispaniola. Falciparum malaria from other areas should not be treated with these older drugs, and decisions regarding chemoprophylaxis should follow the same geographic considerations.

ACTs, all including a short-acting artemisinin and longer-acting partner drug, are first-line therapies in nearly all endemic countries. WHO recommends six ACTs to treat falciparum malaria (Table 35–3), but the efficacy of these regimens varies. Quinine generally remains effective for falciparum malaria, but it must be taken for 7 days and is poorly tolerated, and should best be reserved for the treatment of severe malaria and for treatment after another regimen has failed (Table 35–4).

In developed countries, malaria is an uncommon but potentially life-threatening infection of travelers and immigrants, many of whom are nonimmune, so they are at risk for rapid progression to severe disease. Nonimmune individuals with falciparum malaria should generally be admitted to the hospital due to risks of rapid progression of disease. A number of options are available for the treatment of uncomplicated falciparum malaria in the United States (Table 35–4).

C. Severe Malaria

Severe malaria is a medical emergency. Parenteral treatment is indicated for severe malaria, as defined above, and with inability to take oral drugs. With appropriate prompt therapy and supportive care, rapid recoveries may be seen even in very ill individuals.

Intravenous artesunate is approved by the FDA and is the standard of care for severe malaria. It has demonstrated superior efficacy and better tolerability than quinine. Artesunate is administered intravenously in four doses of 2.4 mg/kg over 3 days every 12 hours on day 1, and then daily. If artesunate cannot be obtained promptly, severe malaria should be treated with intravenous quinine (available in most countries but not the United States), intravenous quinidine (no longer available in the United States), or an oral agent until intravenous artesunate is available. In endemic regions, if parenteral therapy is not available, intrarectal administration of artemether or artesunate is also effective. Patients receiving intravenous quinine or quinidine should receive continuous cardiac monitoring; if QTc prolongation exceeds 25% of baseline, the infusion rate should be reduced. Blood glucose should be monitored every 4–6 hours, and 5–10% dextrose may be coadministered to decrease the likelihood of hypoglycemia.

Appropriate care of severe malaria includes maintenance of fluids and electrolytes; respiratory and hemodynamic support; and consideration of blood transfusions, anticonvulsants, antibiotics for bacterial infections, and hemofiltration or hemodialysis. Exchange transfusion is sometimes used for those with high parasitemia (greater than 5–10%), but beneficial effects have not clearly been demonstrated.

D. Antimalarial Drugs

1. Chloroquine—Chloroquine remains the drug of choice for the treatment of sensitive *P. falciparum* and other species of malaria parasites (Table 35–4). Chloroquine is active against erythrocytic parasites of all human malaria species. It does not eradicate hepatic stages, so it must be used with primaquine to eradicate *P. vivax* and *P. ovale* infections. Chloroquine-resistant *P. falciparum* is widespread in nearly all areas of the world with falciparum malaria, with the exceptions of Central America west of the Panama Canal and Hispaniola. Chloroquine-resistant *P. vivax* has been reported from a number of areas, most notably Southeast Asia and Oceania.

Chloroquine is the drug of choice for the treatment of non-falciparum and sensitive falciparum malaria. It rapidly terminates fever (in 24–48 hours) and clears parasitemia (in 48–72 hours) caused by sensitive parasites. Chloroquine is also the preferred chemoprophylactic agent in malarious regions without resistant falciparum malaria.

Chloroquine is usually well tolerated, even with prolonged use. Pruritus is common, primarily in Africans. Nausea, vomiting, abdominal pain, headache, anorexia, malaise, blurring of vision, and urticaria are uncommon. Dosing after meals may reduce some adverse events.

Table 35–3. WHO recommendations for the treatment of uncomplicated falciparum malaria.

Regimen	Notes
Artemether-lumefantrine (Coartem, Riamet)	Coformulated, first-line therapy in many countries. Approved in the United States.
Artesunate-amodiaquine (ASAQ)	Coformulated, first-line therapy in multiple African countries.
Artesunate-mefloquine	First-line therapy in parts of Southeast Asia and South America but efficacy decreasing in parts of Thailand.
Artesunate-pyronaridine	Coformulated. Most recently approved regimen; used in some Southeast Asian countries.
Artesunate-sulfadoxine-pyrimethamine	First-line in some countries, but efficacy lower than other regimens in most areas.
Dihydroartemisinin-piperaquine	Coformulated. First-line in some countries, but efficacy decreasing in parts of Southeast Asia.

Data from World Health Organization: Guidelines for the Treatment of Malaria. World Health Organization. Geneva 2015.

Table 35–4. Treatment of malaria.

Clinical Setting	Drug Therapy ¹	Alternative Drugs
Chloroquine-sensitive <i>Plasmodium falciparum</i> and <i>Plasmodium malariae</i> infections	Chloroquine phosphate, 1 g at 0 hours, then 500 mg at 6, 24, and 48 hours or— Chloroquine phosphate, 1 g at 0 hours and 24 hours, then 0.5 g at 48 hours	
<i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> infections	Chloroquine (as above), then (if G6PD normal) primaquine, 30-mg base daily for 14 days or tafenoquine 300 mg once	For infections from Indonesia, Papua New Guinea, and other areas with suspected resistance: therapies listed for uncomplicated chloroquine-resistant <i>P falciparum</i> plus primaquine
Uncomplicated infections with chloroquine-resistant <i>P falciparum</i>	Coartem (artemether 20 mg, lumefantrine 120 mg), four tablets twice daily for 3 days or— Malarone, four tablets (total of 1 g of atovaquone, 400 mg of proguanil) daily for 3 days or— Quinine sulfate, 650 mg three times daily for 3–7 days Plus one of the following (when quinine given for < 7 days) Doxycycline, 100 mg twice daily for 7 days or— Clindamycin, 600 mg twice daily for 7 days	Mefloquine, 15 mg/kg once or 750 mg, then 500 mg in 6–8 hours or— Dihydroartemisinin-piperaquine ² (dihydroartemisinin 40 mg, piperaquine 320 mg), 4 tablets daily for 3 days or— ASAQ ² (artesunate 100 mg, amodiaquine 270 mg), two tablets daily for 3 days
Severe or complicated infections with <i>P falciparum</i>	Artesunate 2.4 mg/kg intravenously every 12 hours for 1 day, then daily ³	Quinidine gluconate, ^{4,5} 10 mg/kg intravenously over 1–2 hours, then 0.02 mg/kg intravenously/min or— Quinidine gluconate, ^{4,5} 15 mg/kg intravenously over 4 hours, then 7.5 mg/kg intravenously over 4 hours every 8 hours or— Quinine dihydrochloride, ^{2,4,5} 20 mg/kg intravenously over 4 hours, then 10 mg/kg intravenously every 8 hours or— Artemether ^{2,3} 3.2 mg/kg intramuscularly, then 1.6 mg/kg/day intramuscularly

¹All dosages are oral and refer to salts unless otherwise indicated. See text for additional information on all agents, including toxicities and cautions. See CDC guidelines (phone: 877-FYI-TRIP; <http://www.cdc.gov/malaria/>) for additional information and pediatric dosing.

²Not available in the United States.

³With all parenteral regimens, change to an oral regimen as soon as the patient can tolerate it.

⁴Cardiac monitoring should be in place during intravenous administration of quinidine or quinine.

⁵Avoid loading doses in persons who have received quinine, quinidine, or mefloquine in the prior 24 hours.

G6PD, glucose-6-phosphate dehydrogenase.

2. Amodiaquine, piperaquine, and pyronaridine—Amodiaquine is a 4-aminoquinoline that is closely related to chloroquine. Amodiaquine has been widely used to treat malaria because of its low cost, limited toxicity, and, in some areas, effectiveness against chloroquine-resistant strains of *P falciparum*. Use of amodiaquine decreased after recognition of rare but serious side effects, notably agranulocytosis, aplastic anemia, and hepatotoxicity. However, serious side effects are rare with short-term use, and artesunate-amodiaquine is one of the standard ACTs recommended to treat falciparum malaria (Table 35–3). Chemoprophylaxis with amodiaquine is best avoided because of increased toxicity with long-term use.

Piperaquine is another 4-aminoquinoline that has been coformulated with dihydroartemisinin in an ACT. Piperaquine appears to be well tolerated and in combination with dihydroartemisinin, offers a highly efficacious therapy for falciparum and vivax malaria. Due to the long half-life of piperaquine (~3 weeks), dihydroartemisinin-piperaquine offers the longest period of posttreatment prophylaxis of available ACTs. However, resistance to piperaquine has emerged in southeast Asia, with consequent treatment failures of dihydroartemisinin-piperaquine in that region.

Pyronaridine is a benzonaphthyridine that was also previously used as a monotherapy to treat malaria in China and acts against many drug-resistant strains of *P falciparum*. The combination of artesunate plus pyronaridine has

shown excellent efficacy against falciparum and vivax malaria and has been well tolerated, although elevated transaminases can be seen.

3. Mefloquine—Mefloquine is effective against many chloroquine-resistant strains of *P falciparum* and against other malarial species. Although toxicity is a concern, mefloquine is also a recommended chemoprophylactic drug. Resistance to mefloquine has been reported sporadically from many areas, but it appears to be uncommon except in regions of Southeast Asia with high rates of multidrug resistance (especially border areas of Thailand).

For treatment of uncomplicated malaria, mefloquine can be administered as a single dose or in two doses over 1 day. It is used in combination with artesunate for falciparum malaria, although resistance limits efficacy in Southeast Asia. It should be taken with meals and swallowed with a large amount of water. Mefloquine is recommended by the CDC for chemoprophylaxis in all malarious areas except those with no chloroquine resistance (where chloroquine is preferred) and some rural areas of Southeast Asia with a high prevalence of mefloquine resistance.

Adverse effects with weekly dosing of mefloquine for chemoprophylaxis include nausea, vomiting, dizziness, sleep and behavioral disturbances, epigastric pain, diarrhea, abdominal pain, headache, rash and, uncommonly, seizures and psychosis. There is an FDA black box warning about neuropsychiatric toxicity, possibly including rare, irreversible effects. Mefloquine should be avoided in persons with histories of psychiatric disease or seizures.

Adverse effects are more common (up to 50% of treatments) with the higher dosages of mefloquine required for treatment. These effects may be lessened by splitting administration into two doses separated by 6–8 hours. Serious neuropsychiatric toxicities (depression, confusion, acute psychosis, or seizures) have been reported in less than 1 in 1000 treatments, but some authorities believe that these are more common. Mefloquine can also alter cardiac conduction, and so it should not be coadministered with quinine, quinidine, or halofantrine, and caution is required if these drugs are used to treat malaria after mefloquine chemoprophylaxis. Mefloquine is generally considered safe in young children and pregnant women.

4. Quinine and quinidine—Quinine dihydrochloride and quinidine gluconate are effective therapies for falciparum malaria, especially severe disease, although toxicity concerns complicate therapy (Table 35–4). Quinine acts rapidly against the four species of human malaria parasites. Quinidine, the dextrorotatory stereoisomer of quinine, is at least as effective as quinine in the treatment of severe falciparum malaria, but is no longer available in the United States.

Resistance of *P falciparum* to quinine is common in some areas of Southeast Asia, where the drug may fail if used alone to treat falciparum malaria. However, quinine still provides at least a partial therapeutic effect in most patients.

Quinine and quinidine are effective treatments for severe falciparum malaria, although intravenous artesunate is the standard of care. The drugs can be administered in divided doses or by continuous intravenous infusion;

treatment should begin with a loading dose to rapidly achieve effective plasma concentrations. Intravenous quinine and quinidine should be administered with cardiac monitoring because of their cardiac toxicity and the relative unpredictability of their pharmacokinetics. Therapy should be changed to an oral agent as soon as the patient has improved and can tolerate oral medications.

In areas without newer combination regimens, oral quinine sulfate is an alternative first-line therapy for uncomplicated falciparum malaria, although poor tolerance may limit compliance. Quinine is commonly used with a second drug (most often doxycycline) to shorten the duration of use (to 3 days) and to limit toxicity. Therapeutic dosages of quinine and quinidine commonly cause tinnitus, headache, nausea, dizziness, flushing, and visual disturbances. Hematologic abnormalities include hemolysis (especially with G6PD deficiency), leukopenia, agranulocytosis, and thrombocytopenia. Therapeutic doses may cause hypoglycemia through stimulation of insulin release; this is a particular problem in severe infections and in pregnant patients, who have increased sensitivity to insulin. Overly rapid infusions can cause severe hypotension. ECG abnormalities (QT prolongation) are fairly common, but dangerous arrhythmias are uncommon when the drugs are administered appropriately. Quinine should not be given concurrently with mefloquine and should be used with caution in a patient who has previously received mefloquine.

5. Primaquine and tafenoquine—Primaquine phosphate, a synthetic 8-aminoquinoline, is the drug of choice for the eradication of dormant liver forms of *P vivax* and *P ovale* (Table 35–4). Primaquine is active against hepatic stages of all human malaria parasites. This action is optimal soon after therapy with chloroquine or other agents. Primaquine also acts against erythrocytic stage parasites, although this activity is too weak for the treatment of active disease, and against gametocytes. The addition of a single low dose of primaquine in conjunction with an ACT in G6PD-normal patients with falciparum malaria is a strategy to lower transmission to mosquitoes.

For *P vivax* and *P ovale* infections, chloroquine or other drugs are used to eradicate erythrocytic forms, and if the G6PD level is normal, a 14-day course of primaquine (52.6 mg primaquine phosphate [30 mg base] daily) is initiated to eradicate liver hypnozoites and prevent a subsequent relapse. Some strains of *P vivax*, particularly in New Guinea and Southeast Asia, are relatively resistant to primaquine, and the drug may fail to eradicate liver forms.

Standard chemoprophylaxis does not prevent a relapse of *P vivax* or *P ovale* infections, since liver hypnozoites are not eradicated by chloroquine or other standard treatments. To diminish the likelihood of relapse, some authorities advocate the use of a treatment course of primaquine after the completion of travel to an endemic area. Primaquine can also be used for chemoprophylaxis to prevent *P falciparum* and *P vivax* infection in persons with normal levels of G6PD.

Primaquine in recommended doses is generally well tolerated. It infrequently causes nausea, epigastric pain,

abdominal cramps, and headache, especially when taken on an empty stomach. Rare adverse effects include leukopenia, agranulocytosis, leukocytosis, and cardiac arrhythmias. Standard doses of primaquine may cause hemolysis or methemoglobinemia (manifested by cyanosis), especially in persons with G6PD deficiency or other hereditary metabolic defects. Patients should be tested for G6PD deficiency before primaquine is prescribed. Primaquine should be discontinued if there is evidence of hemolysis or anemia and should be avoided in pregnancy.

Tafenoquine, an 8-aminoquinoline, has a much longer half-life than primaquine. These two medications share the risk of hemolysis with G6PD deficiency and probably other toxicities; tafenoquine should not be used during pregnancy or in those with G6PD deficiency. Tafenoquine is FDA-approved for patients at least 16 years of age for two indications, but with different formulations, marketed by different companies. To eliminate hepatic stages of *P vivax*, a single dose (Krintafel, two 150-mg tablets once daily) is taken with food soon after initiation of primary therapy (with chloroquine or other agents). For malaria chemoprophylaxis, the drug (Arakoda, two 100-mg tablets) is taken once daily for 3 days and then weekly until 1 week after the last exposure.

6. Inhibitors of folate synthesis—Inhibitors of two parasite enzymes involved in folate metabolism, dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS), are used, generally in combination regimens, for the treatment and prevention of malaria, although the drugs are rather slow acting and limited by resistance.

Fansidar is a fixed combination of sulfadoxine (500 mg) and pyrimethamine (25 mg). It is not advised for chemoprophylaxis due to rare serious side effects with long-term dosing. For treatment, advantages of sulfadoxine-pyrimethamine include ease of administration (a single oral dose) and low cost. However, resistance is a major problem.

Sulfadoxine-pyrimethamine plus artesunate has shown efficacy for malaria treatment in some areas but is best replaced by more effective ACTs. Sulfadoxine-pyrimethamine is recommended by WHO for monthly preventive therapy in pregnant women in areas of high endemicity, although its efficacy is limited by resistance. Amodiaquine plus sulfadoxine-pyrimethamine is recommended monthly during the rainy season for chemoprevention in regions of West Africa with seasonal malaria transmission and limited drug resistance. Another antifolate combination, trimethoprim-sulfamethoxazole (TMP-SMZ), is widely used to prevent coinfections in patients infected with HIV, and it offers partial protection against malaria.

7. Artemisinins—Artemisinin (qinghaosu) is a sesquiterpene lactone endoperoxide, the active component of an herbal medicine that has been used for various indications in China for over 2000 years. Analogs have been synthesized to increase solubility and improve antimalarial efficacy. The most important of these analogs are artesunate, artemether, and dihydroartemisinin. WHO encourages availability of oral artemisinins only in coformulated combination regimens.

Artemisinins act very rapidly against all erythrocytic-stage human malaria parasites. Of concern, delayed clearance of parasites and clinical failures have been seen after treatment with artesunate in parts of Southeast Asia, heralding the emergence of artemisinin resistance in this region.

Artemisinins play a vital role in the treatment of malaria, including multidrug-resistant *P falciparum* malaria. Due to their short plasma half-lives, recrudescence rates are unacceptably high after short-course therapy, leading to approved use only as *initial* therapy for severe malaria and in ACTs for uncomplicated malaria. The ACTs that are currently most advocated in Africa are artesunate plus amodiaquine (ASAQ) and artemether plus lumefantrine (Coartem), each of which is available as a coformulated product. Another ACT, artesunate plus mefloquine, is used mostly outside of Africa; its efficacy may be declining in parts of Asia. Dihydroartemisinin-piperazine has shown excellent efficacy and is the first-line regimen in some countries in Southeast Asia, but efficacy has declined in Cambodia due to decreased activity of both components of the regimen. The newest approved ACT, artesunate-pyronaridine, is approved in some countries. Other ACTs not recommended by the WHO are available in some countries and have shown good efficacy in limited studies, including arterolane-piperazine, artemisinin-piperazine, and artemisinin-naphthoquine.

In studies of severe malaria, intramuscular artemether was at least as effective as intramuscular quinine, and intravenous artesunate was superior to intravenous quinine in terms of efficacy and tolerability. Thus, the standard of care for severe malaria is intravenous artesunate, when it is available, although parenteral quinine and quinidine remain acceptable alternatives. Artesunate and artemether have also been effective in the treatment of severe malaria when administered rectally, offering a valuable treatment modality when parenteral therapy is not available.

Artemisinins are very well tolerated. The most commonly reported adverse effects have been nausea, vomiting, and diarrhea, which may often be due to acute malaria, rather than drug toxicity. Neutropenia, anemia, hemolysis, and elevated levels of liver enzymes have been noted rarely. Hemolysis may occur weeks after therapy with intravenous artesunate. Artemisinins are teratogenic in animals, but with good safety seen in humans, and the importance of effectively treating malaria during pregnancy, the WHO recommends ACTs to treat uncomplicated malaria and intravenous artesunate to treat complicated malaria during all trimesters of pregnancy.

8. Atovaquone plus proguanil (Malarone)—Atovaquone, a hydroxynaphthoquinone, is not effective when used alone, due to rapid development of drug resistance. However, Malarone, a fixed combination of atovaquone (250 mg) and the antifolate proguanil (100 mg), is highly effective for both the treatment and chemoprophylaxis of *falciparum* malaria, and it is approved for both indications in the United States (Table 35–4). It also appears to be active against other species of malaria parasites. Unlike

Table 35–5. Drugs for the prevention of malaria in travelers.¹

Drug	Use ²	Adult Dosage (all oral) ³
Chloroquine	Areas without resistant <i>Plasmodium falciparum</i>	500 mg weekly
Malarone	Areas with multidrug-resistant <i>P falciparum</i>	1 tablet (250-mg atovaquone/100-mg proguanil) daily
Mefloquine	Areas with chloroquine-resistant <i>P falciparum</i>	250 mg weekly
Doxycycline	Areas with multidrug-resistant <i>P falciparum</i>	100 mg daily
Primaquine ⁴	Terminal prophylaxis of <i>Plasmodium vivax</i> and <i>Plasmodium ovale</i> infections; alternative for <i>P falciparum</i> prophylaxis	30-mg base daily; for terminal prophylaxis take for 14 days after travel; for chemoprevention begin 1–2 days before travel, take during travel and for 7 days after travel
Tafenoquine ⁴	Alternative for <i>P falciparum</i> prophylaxis	200 mg once daily for 3 days and then weekly until 1 week after last exposure

¹Recommendations may change, as resistance to all available drugs is increasing. See text for additional information on toxicities and cautions. For additional details and pediatric dosing, see CDC guidelines (phone: 800-CDC-INFO; <http://wwwnc.cdc.gov/travel/>). Travelers to remote areas should consider carrying effective therapy (see text) for use if a febrile illness develops, and they cannot reach medical attention quickly.

²Areas without known chloroquine-resistant *P falciparum* are Central America west of the Panama Canal, Haiti, Dominican Republic, Egypt, and most malarious countries of the Middle East. Malarone or mefloquine is currently recommended for other malarious areas except for border areas of Thailand, where doxycycline is recommended.

³For drugs other than primaquine, begin 1–2 weeks before departure (except 2 days before for doxycycline and Malarone) and continue for 4 weeks after leaving the endemic area (except 1 week for Malarone). All dosages refer to salts unless otherwise indicated.

⁴Screen for glucose-6-phosphate dehydrogenase deficiency before using primaquine.

Modified, with permission, from Katzung BG. *Basic & Clinical Pharmacology*, 14th edition. McGraw-Hill, 2018.

most other antimalarials, Malarone provides activity against both erythrocytic and hepatic stage parasites.

For treatment, Malarone is given at an adult dose of four tablets daily for 3 days (Table 35–5). For chemoprophylaxis, Malarone must be taken daily. It has an advantage over mefloquine and doxycycline in requiring shorter durations of treatment before and after the period at risk for malaria transmission, due to activity against liver-stage parasites. It should be taken with food.

Malarone is generally well tolerated. Adverse effects include abdominal pain, nausea, vomiting, diarrhea, headache, and rash, and these are more common with the higher dose required for treatment. Reversible elevations in liver enzymes have been reported. The safety of atovaquone in pregnancy is unknown.

9. Antibiotics—A number of antibiotics in addition to the folate antagonists and sulfonamides are slow-acting antimalarials. None of the antibiotics should be used as single agents for the treatment of malaria due to their slow rate of action.

Doxycycline is commonly used in the treatment of falciparum malaria in conjunction with quinidine or quinine, allowing a shorter and better-tolerated course of those drugs (Table 35–4). Doxycycline is also a standard chemoprophylactic drug, especially for use in areas of Southeast Asia with high rates of resistance to other antimalarials, including mefloquine. Doxycycline side effects include gastrointestinal symptoms, candidal vaginitis, and photosensitivity. The drug should be taken while upright with a large amount of water to avoid esophageal irritation. Clindamycin can be used in conjunction with quinine or quinidine in those for whom doxycycline is not recommended, such as children and pregnant women

(Table 35–4). The most common toxicities with clindamycin are gastrointestinal.

10. Lumefantrine—Lumefantrine, an aryl alcohol related to halofantrine, is available only as a fixed-dose combination with artemether (Coartem or Riamet). Oral absorption is highly variable and improved when the drug is taken with food. Use of Coartem with a fatty meal is recommended. Coartem is highly effective for the treatment of falciparum malaria, but it requires twice-daily dosing. Despite this limitation, due to its reliable efficacy against falciparum malaria, Coartem is the first-line therapy for malaria in many malarious countries. Coartem is well tolerated; side effects include headache, dizziness, loss of appetite, gastrointestinal symptoms, and palpitations. Importantly, Coartem does not generally cause QT prolongation or the serious cardiac toxicity seen with halofantrine.

► Prevention

Malaria is transmitted by night-biting anopheline mosquitoes. Bed nets, in particular nets treated with permethrin insecticides, are heavily promoted as inexpensive means of antimalarial protection, but effectiveness varies in part due to widespread insecticide resistance. Indoor spraying of insecticides is generally highly effective in Africa but limited by resource constraints.

Extensive efforts are underway to develop a malaria vaccine, but a vaccine offering a high level of protection is not anticipated in the near future. RTS,S vaccine, which is based on a sporozoite antigen, is the most advanced vaccine candidate. Multiple clinical trials showed about 25–50% protection against malaria in children in the year after immunization, but lower levels of protection in very

young children, in areas of highest malaria exposure, and over longer periods of time. Seasonal malaria immunization, using short-acting vaccines during the high transmission season, is being investigated. Other approaches under study include vaccines containing erythrocytic, liver-stage, and sexual-stage antigens, and use of radiation-attenuated or molecularly attenuated sporozoites.

When travelers from nonendemic to endemic countries are counseled on the prevention of malaria, it is imperative to emphasize measures to prevent mosquito bites (insect repellents, insecticides, and bed nets), since parasites are increasingly resistant to multiple drugs and no chemoprophylactic regimen is fully protective. Chemoprophylaxis is recommended for all travelers from nonendemic regions to endemic areas, although risks vary greatly for different locations, and some tropical areas entail no risk; specific recommendations for travel to different locales are available from the CDC (www.cdc.gov; 877-FYI-TRIP). Recommendations from the CDC include the use of chloroquine for chemoprophylaxis in the few areas with only chloroquine-sensitive malaria parasites (principally the Caribbean and Central America west of the Panama Canal), and Malarone, mefloquine, or doxycycline for other areas (Table 35–5). Primaquine and tafenoquine are also effective but not used as often. In some circumstances, it may be appropriate for travelers to not use chemoprophylaxis but to carry supplies of drugs with them in case a febrile illness develops and medical attention is unavailable. Regimens for self-treatment include ACTs, Malarone, and quinine. Most authorities do not recommend routine terminal prophylaxis with primaquine to eradicate dormant hepatic stages of *P vivax* and *P ovale* after travel, but this may be appropriate in some circumstances, especially for travelers with major exposure to these parasites.

Regular chemoprophylaxis is not a standard management practice in developing world populations due to the expense and potential toxicities of long-term therapy. However, the strategy of intermittent preventive therapy, whereby at-risk populations (in particular pregnant women and children) receive antimalarial therapy at set intervals, may decrease the incidence of malaria while allowing antimalarial immunity to develop. During pregnancy, intermittent preventive therapy with sulfadoxine-pyrimethamine, provided once during both the second and third trimesters, has improved pregnancy outcomes. With increasing resistance, the preventive efficacy of sulfadoxine-pyrimethamine is likely falling, and the long-acting ACT dihydroartemisinin-piperaquine is a promising replacement. In areas with seasonal malaria transmission and limited drug resistance, principally the Sahel subregion of West Africa, the policy is to administer amodiaquine and sulfadoxine-pyrimethamine to children monthly during the transmission season.

► Prognosis

When treated appropriately, uncomplicated malaria generally responds well, with resolution of fevers within 1–2 days and a mortality of about 0.1%. Severe malaria can commonly progress to death, but many children respond well to therapy. In the developed world, mortality from malaria is mostly in adults, and often follows extended illnesses and

secondary complications long after eradication of the malarial infection. Pregnant women are at particular risk during their first pregnancy. Malaria in pregnancy also increases the likelihood of poor pregnancy outcomes, with increased prematurity, low birth weight, and mortality.

► When to Refer

Referral to an expert on infectious diseases or travel medicine is important with all cases of malaria in the United States, and in particular for falciparum malaria; referral should not delay initial diagnosis and therapy, since delays in therapy can lead to severe illness or death.

► When to Admit

- Admission for non-falciparum malaria is warranted only if specific problems that require hospital management are present.
- Patients with falciparum malaria are generally admitted because the disease can progress rapidly to severe illness; exceptions may be made with individuals who are from malaria-endemic areas, and thus expected to have a degree of immunity, who are without evidence of severe disease, and who are judged able to return promptly for medical attention if their disease progresses.

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BABESIOSIS

- 
- ### ESSENTIALS OF DIAGNOSIS
- History of tick bite or exposure to ticks.
 - Fever, flu-like symptoms, anemia.
 - Intraerythrocytic parasites on Giemsa-stained blood smears.
 - Positive serologic tests.

► General Considerations

Babesiosis is an uncommon intraerythrocytic infection caused mainly by two *Babesia* species and transmitted by *Ixodes* ticks. In the United States, hundreds of cases of babesiosis have been reported, and infection is caused by *Babesia microti*, which also infects wild mammals. Most babesiosis in the United States occurs in the coastal northeast, with some cases also in the upper midwest, following the geographic range of the vector *Ixodes scapularis*, and Lyme disease and anaplasmosis, which are spread by the same vector. The incidence of the disease appears to be increasing in some areas. Babesiosis is caused by *Babesia divergens* in Europe and by *Babesia venatorum* in China. Babesiosis due to *Babesia duncani* and other Babesia-like organisms have been reported uncommonly from the western United States. Babesiosis can also be transmitted by blood transfusion, but blood supplies are not screened. A survey of a large set of blood samples from endemic regions of the United States identified ~0.4% as potentially infectious for *B microti*.

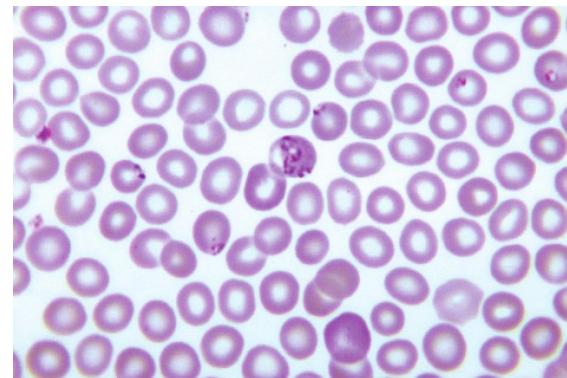
► Clinical Findings

A. Symptoms and Signs

Serosurveys suggest that asymptomatic infections are common in endemic areas. With *B microti* infections, symptoms appear 1 to several weeks after a tick bite; parasitemia is evident after 2–4 weeks. Patients usually do not recall the tick bite. The typical flu-like illness develops gradually and is characterized by fever, malaise, fatigue, headache, anorexia, and myalgia. Other findings may include nausea, vomiting, abdominal pain, arthralgia, sore throat, depression, emotional lability, anemia, thrombocytopenia, elevated transaminases, and splenomegaly. Parasitemia may continue for months to years, with or without symptoms, and the disease is usually self-limited. Severe complications are most likely to occur in older persons or in those who have had splenectomy. Serious complications include respiratory failure, hemolytic anemia, disseminated intravascular coagulation, heart failure, and acute kidney injury. In a study of hospitalized patients, the mortality rate was 6.5%. Most recognized *B divergens* infections in Europe have been in patients who have had splenectomy. These infections progress rapidly with high fever, severe hemolytic anemia, jaundice, hemoglobinuria, and acute kidney injury, with death rates over 40%.

B. Laboratory Findings

Identification of the intraerythrocytic parasite on Giemsa-stained blood smears establishes the diagnosis (Figure 35–6). These can be confused with malaria parasites, but the morphology is distinctive. Repeated smears are often necessary because well under 1% of erythrocytes may be infected, especially early in infection, although parasitemias can exceed 10%. Diagnosis can also be made by PCR, which is more sensitive than blood smear. An indirect immunofluorescent antibody test for *B microti* is available from the CDC; antibody is detectable within 2–4 weeks after the onset of symptoms and persists for



▲ **Figure 35–6.** Blood smear showing *Babesia* spp. rings with basophilic stippling. (From Dr. Mae Melvin, Public Health Image Library, CDC.)

months, and a fourfold increase in antibody titer between acute and convalescent sera confirms acute infection.

► Treatment

Most patients have a mild illness and recover without therapy. Standard therapy for mild to moderate disease is a 7-day course of atovaquone (750 mg orally every 12 hours) plus azithromycin (600 mg orally once daily), which is equally effective and better tolerated than the alternative regimen, a 7-day course of quinine (650 mg orally three times daily) plus clindamycin (600 mg orally three times daily). However, there is more experience using quinine plus clindamycin, and this regimen is recommended by some experts for severe disease. Exchange transfusion has been used successfully in severely ill asplenic patients and those with parasitemia greater than 10%.

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TOXOPLASMOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Infection confirmed by isolation of *Toxoplasma gondii* or identification of tachyzoites in tissue or body fluids.

Primary infection

- ▶ Fever, malaise, headache, sore throat.
- ▶ Lymphadenopathy.
- ▶ Positive IgG and IgM serologic tests.

Congenital infection

- ▶ After acute infection of seronegative mothers, CNS abnormalities and retinochoroiditis seen in offspring.

Infection in immunocompromised persons

- ▶ Reactivation leads to encephalitis, retinochoroiditis, pneumonitis, myocarditis.
- ▶ Positive IgG but negative IgM serologic tests.

► General Considerations

T gondii, an obligate intracellular protozoan, is found worldwide in humans and in many species of mammals and birds. The definitive hosts are cats. Humans are infected after ingestion of cysts in raw or undercooked meat, ingestion of oocysts in food or water contaminated by cats, transplacental transmission of trophozoites or, rarely, direct inoculation of trophozoites via blood transfusion or organ transplantation. *Toxoplasma* seroprevalence varies widely. It has decreased in the United States to less than 20%, but it is much higher in other countries in both the developed and developing worlds, where it may exceed 80%. In the United States, *T gondii* is estimated to infect 1.1 million persons each year, with resultant chorioretinitis developing in 21,000 and vision loss in 4800.

► Clinical Findings

A. Symptoms and Signs

The clinical manifestations of toxoplasmosis may be grouped into four syndromes.

1. Primary infection in the immunocompetent person—

After ingestion, *T gondii* infection progresses from the gastrointestinal tract to lymphatics, and then dissemination. Most acute infections are asymptomatic. About 10–20% are symptomatic after an incubation period of 1–2 weeks. Acute infections in immunocompetent persons typically present as mild, febrile illnesses that resemble infectious mononucleosis. Nontender cervical or diffuse lymphadenopathy may persist for weeks to months. Systemic findings may include fever, malaise, headache, sore throat, rash, myalgias, hepatosplenomegaly, and atypical lymphocytosis. Rare severe manifestations are pneumonitis, meningoencephalitis, hepatitis, myocarditis, polymyositis, and retinochoroiditis. Symptoms may fluctuate, but most patients recover spontaneously within at most a few months.

2. Congenital infection—Congenital transmission occurs as a result of infection, which may be symptomatic or asymptomatic, in a nonimmune woman during pregnancy. Fetal infection follows maternal infection in 30–50% of cases, but this risk varies by trimester: 10–25% during the first, 30–50% during the second, and 60% or higher during the third trimester. In the United States, an estimated 400 to 4000 congenital infections occur yearly. While the risk of fetal infection increases, the risk of severe fetal disease decreases over the course of pregnancy. Early fetal infections commonly lead to spontaneous abortion, stillbirths, or severe neonatal disease, including neurologic manifestations. Retinochoroiditis and other sight-threatening eye lesions may develop. Infections later in pregnancy less commonly lead to major fetal problems. Most infants

appear normal at birth, but they may have subtle abnormalities and progress to symptoms and signs of congenital toxoplasmosis later in life.

3. Retinochoroiditis—The most common late presentation of congenital toxoplasmosis is retinochoroiditis, which presents weeks to years after congenital infection, commonly in teenagers or young adults. Retinochoroiditis is also seen in persons who acquire infection early in life, and these patients more often present with unilateral disease. Uveitis is also seen. Disease presents with pain, photophobia, and visual changes, usually without systemic symptoms. Signs and symptoms eventually improve, but visual defects may persist. Rarely, progression may result in glaucoma and blindness.

4. Disease in the immunocompromised person—Reactivated toxoplasmosis occurs in patients with AIDS, cancer, or those given immunosuppressive drugs. In patients with advanced AIDS, the most common manifestation is encephalitis, with multiple necrotizing brain lesions. The encephalitis usually presents subacutely, with fever, headache, altered mental status, focal neurologic findings, and other evidence of brain lesions. Less common manifestations of toxoplasmosis in patients with AIDS are chorioretinitis and pneumonitis. Chorioretinitis presents with ocular pain and alterations in vision. Pneumonitis presents with fever, cough, and dyspnea. Toxoplasmosis can develop in recipients of solid organ or bone marrow transplants due to reactivation or, more rarely, transmission of infection. Reactivation also can occur in those with hematologic malignancies or treated with immunosuppressive drugs. With primary or reactivated disease in those with immunodeficiency due to malignancy or immunosuppressive drugs, toxoplasmosis is similar to that in individuals with AIDS, but pneumonitis and myocarditis are more common.

B. Diagnostic Testing

1. Identification of parasites—Organisms can be seen in tissue or body fluids, although they may be difficult to identify; special staining techniques can facilitate identification. The demonstration of tachyzoites indicates acute infection; cysts may represent either acute or chronic infection. With lymphadenopathy due to toxoplasmosis, examination of lymph nodes usually does not show organisms. Parasite identification can also be made by inoculation of tissue culture or mice. PCR can be used for sensitive identification of organisms in amniotic fluid, blood, CSF, aqueous humor, and bronchoalveolar lavage fluid.

2. Serologic diagnosis—Multiple serologic methods are used, including the Sabin-Feldman dye test, enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody test, and agglutination tests. IgG antibodies are seen within 1–2 weeks of infection and usually persist for life. IgM antibodies peak earlier than IgG and decline more rapidly, although they may persist for years. In immunocompromised individuals in whom reactivation is suspected, a positive IgG assay indicates distant infection, and thus the potential for reactivated disease; a negative IgG

argues strongly against reactivation toxoplasmosis. With reactivation in immunocompromised persons, IgM tests are generally negative.

3. During pregnancy and in newborns—Conversion from a negative to positive serologic test or rising titers are suggestive of acute infection, but tests are not routinely performed during pregnancy. When pregnant women are screened, negative IgG and IgM assays exclude active infection, but indicate the risk of infection during the pregnancy. Positive IgG with negative IgM is highly suggestive of chronic infection, with no risk of congenital disease unless the mother is severely immunocompromised. A positive IgM test is concerning for new infection because of the risk of congenital disease. Confirmatory testing should be performed before consideration of treatment or possible termination of pregnancy due to the limitations of available tests. Tests of the avidity of anti-IgG antibodies can be helpful, but a battery of tests is needed for confirmation of acute infection during pregnancy. When acute infection during pregnancy is suspected, PCR of amniotic fluid offers a sensitive assessment for congenital disease. In newborns, positive IgM or IgA antibody tests are indicative of congenital infection, although the diagnosis is not ruled out by a negative test. Positive IgG assays may represent transfer of maternal antibodies without infection of the infant, but persistence of positive IgG beyond 12 months of age is diagnostic of congenital infection. PCR of blood, CSF, or urine can also be helpful for early diagnosis of congenital disease.

4. In immunocompetent individuals—Individuals with a suggestive clinical syndrome should be tested for IgG and IgM antibodies. Seroconversion, a 16-fold rise in antibody titer, or an IgM titer greater than 1:64 is suggestive of acute infection, although false-positive results may occur. Acute infection can also be diagnosed by detection of tachyzoites in tissue, culture of organisms, or PCR of blood or body fluids. Histologic evaluation of lymph nodes can show characteristic morphology, with or without organisms.

5. In immunodeficient individuals—A presentation consistent with toxoplasmic encephalitis warrants imaging of the brain. CT and MRI scans typically show multiple ring-enhancing cerebral lesions, most commonly involving the corticomedullary junction and basal ganglia. MRI is the more sensitive imaging modality. In AIDS patients with a positive IgG serologic test and no recent antitoxoplasma or antiviral therapy, the predictive value of a typical imaging study is about 80%. The other common diagnosis in this setting is CNS lymphoma, which more typically causes a single brain lesion. The differential diagnosis also includes tuberculoma, bacterial brain abscess, fungal abscess, and carcinoma. Diagnosis of CNS toxoplasmosis is most typically made after a therapeutic trial, with clinical and radiologic improvement expected within 2–3 weeks. Definitive diagnosis requires brain biopsy and search for organisms and typical histology. In retinochoroiditis, funduscopic examination shows vitreous inflammatory reaction, white retinal lesions, and pigmented scars. Diagnosis of other clinical entities in immunocompromised individuals is generally based on histology.

► Treatment

A. Approach to Treatment

Therapy is generally not necessary in immunocompetent persons, since primary illness is self-limited. However, for severe, persistent, or visceral disease, treatment for 2–4 weeks may be considered. Treatment is appropriate for primary infection during pregnancy because the risk of fetal transmission or the severity of congenital disease may be reduced. For retinochoroiditis, most episodes are self-limited, and opinions vary on indications for treatment. Treatment is often advocated for episodes with decreases in visual acuity, multiple or large lesions, macular lesions, significant inflammation, or persistence for over a month. Immunocompromised patients with active infection must be treated. For those with transient immunodeficiency, therapy can be continued for 4–6 weeks after cessation of symptoms. For those with persistent immunodeficiency, such as AIDS patients, full therapy for 4–6 weeks is followed by maintenance therapy with lower doses of drugs. Immunodeficient patients who are asymptomatic but have a positive IgG serologic test should receive long-term chemoprophylaxis.

B. Medications

Drugs for toxoplasmosis are active only against tachyzoites, so they do not eradicate infection. Standard therapy is the combination of pyrimethamine (200-mg loading dose, then 50–75 mg [1 mg/kg] orally once daily) plus sulfadiazine (1–1.5 g orally four times daily), with folinic acid (10–20 mg orally once daily) to prevent bone marrow suppression. Patients should be screened for a history of sulfonamide sensitivity (skin rashes, gastrointestinal symptoms, hepatotoxicity). To prevent sulfonamide crystal-induced nephrotoxicity, good urinary output should be maintained. Pyrimethamine side effects include headache and gastrointestinal symptoms. Even with folinic acid therapy, bone marrow suppression may occur; platelet and white blood cell counts should be monitored at least weekly. A first-line alternative is clindamycin (600 mg orally four times daily) replacing sulfadiazine as the standard therapy regimen. Another alternative is TMP-SMZ. Pyrimethamine is not used during the first trimester of pregnancy due to its teratogenicity. Standard therapy for acute toxoplasmosis during pregnancy is spiramycin (1 g orally three times daily until delivery) to decrease the risk of fetal infection; it reduces the frequency of transmission to the fetus by about 60%. Spiramycin does not cross the placenta, so when fetal infection is documented or for acute infections late in pregnancy (which commonly lead to fetal transmission) treatment with combination regimens as described above is indicated.

► Prevention

Prevention of primary infection centers on avoidance of undercooked meat or contact with material contaminated by cat feces, particularly for seronegative pregnant women and immunocompromised persons. Irradiation, cooking to 66°C, or freezing to –20°C kills tissue cysts. Thorough

cleaning of hands and surfaces is needed after contact with raw meat or areas contaminated by cats. Oocysts passed in cat feces can remain infective for a year or more, but fresh oocysts are not infective for 48 hours. For best protection, litter boxes should be changed daily and soaked in boiling water for 5 minutes, gloves should be worn when gardening, fruits and vegetables should be thoroughly washed, and ingestion of dried meat should be avoided.

Universal screening of pregnant women for *T gondii* antibodies is conducted in some countries but not the United States. Pregnant women should ideally have their serum examined for IgG and IgM antibody, and those with negative titers should adhere to the prevention measures described above. Seronegative women who continue to have environmental exposure should undergo repeat serologic screening several times during pregnancy.

For immunocompromised individuals, chemoprophylaxis to prevent primary or reactivated infection is warranted. For hematopoietic cell transplant recipients and advanced AIDS patients, chemoprophylaxis with TMP-SMZ (one double-strength tablet daily or two tablets three times weekly), used for protection against *Pneumocystis*, is effective against *T gondii*. Alternatives are pyrimethamine plus either sulfadiazine or dapsone (various regimens). In AIDS patients, chemoprophylaxis can be discontinued if antiretroviral therapy leads to immune reconstitution.

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AMEBIASIS

ESSENTIALS OF DIAGNOSIS

- ▶ Organisms or antigen present in stools or abscess aspirate.
- ▶ Positive serologic tests with colitis or hepatic abscess, but these may represent prior infections.
- ▶ Mild to moderate colitis with recurrent diarrhea.
- ▶ Severe colitis: bloody diarrhea, fever, and abdominal pain, with potential progression to hemorrhage or perforation.
- ▶ Hepatic abscess: fever, hepatomegaly, and abdominal pain.

General Considerations

The *Entamoeba* complex contains three morphologically identical species: *Entamoeba dispar* and *Entamoeba moshkovskii*, which are avirulent, and *Entamoeba histolytica*, which may be an avirulent intestinal commensal or lead to serious disease. Disease follows penetration of the intestinal wall, resulting in diarrhea, and with severe

involvement, dysentery or extraintestinal disease, most commonly liver abscess.

E histolytica infections are present worldwide but are most prevalent in subtropical and tropical areas under conditions of crowding, poor sanitation, and poor nutrition. Of the estimated 500 million persons worldwide infected with *Entamoeba*, most are infected with *E dispar* and an estimated 10% with *E histolytica*. The prevalence of *E moshkovskii* is unknown. Mortality from invasive *E histolytica* infections is estimated at 100,000 per year.

Humans are the only established *E histolytica* host. Transmission occurs through ingestion of cysts from fecally contaminated food or water, facilitated by person-to-person spread, flies and other arthropods as mechanical vectors, and use of human excrement as fertilizer. Urban outbreaks have occurred because of common-source water contamination.

Clinical Findings

A. Symptoms and Signs

1. Intestinal amebiasis—In most infected persons, the organism lives as a commensal, and the carrier is without symptoms. With symptomatic disease, diarrhea may begin within a week of infection, although an incubation period of 2–4 weeks is more common, with gradual onset of abdominal pain and diarrhea. Fever is uncommon. Periods of remission and recurrence may last days to weeks or longer. Abdominal examination may show distention, tenderness, hyperperistalsis, and hepatomegaly. Microscopic hematochezia is common. More severe presentations include colitis and dysentery, with worse diarrhea (10–20 stools per day) and bloody stools. With dysentery, physical findings include high fevers, prostration, vomiting, abdominal pain and tenderness, hepatic enlargement, and hypotension. Severe presentations are more common in young children, pregnant women, those who are malnourished, and those receiving corticosteroids. Thus, in endemic regions, corticosteroids should not be started for presumed inflammatory bowel disease without first ruling out amebiasis. Fulminant amebic colitis can progress to necrotizing colitis, intestinal perforation, mucosal sloughing, and severe hemorrhage, with mortality rates over 40%. More long-term complications of intestinal amebiasis include chronic diarrhea with weight loss, which may last for months to years; bowel ulcerations; and amebic appendicitis. Localized granulomatous lesions (amebomas) can present after either dysentery or chronic intestinal infection. Clinical findings include pain, obstructive symptoms, and hemorrhage and may suggest intestinal carcinoma.

2. Extraintestinal amebiasis—The most common extraintestinal manifestation is amebic liver abscess. This can occur with colitis, but more frequently presents without history of prior intestinal symptoms. Patients present with the acute or gradual onset of abdominal pain, fever, an enlarged and tender liver, anorexia, and weight loss. Diarrhea is present in a small number of patients. Physical examination may show intercostal tenderness. Abscesses are most commonly single and in the right lobe of the liver, and they are much more common in men. Without prompt treatment, amebic abscesses may rupture into the pleural,

peritoneal, or pericardial space, which is often fatal. Amebic infections may rarely occur throughout the body, including the lungs, brain, and genitourinary system.

B. Laboratory Findings

Laboratory studies with intestinal amebiasis show leukocytosis and hematochezia, with fecal leukocytes not present in all cases. With extraintestinal amebiasis, leukocytosis and elevated liver function studies are seen.

C. Diagnostic Testing

Diagnosis is typically made by finding *E histolytica* or its antigen or by serologic tests. However, each method has limitations. Molecular diagnosis is possible from multi-pathogen panels, which are sensitive and specific but expensive.

1. Intestinal amebiasis—Diagnosis is most commonly made by identifying organisms in the stool. *E histolytica* and *E dispar* cannot be distinguished, but the identification of amebic trophozoites or cysts in a symptomatic patient is highly suggestive of amebiasis. Stool evaluation for organisms is not highly sensitive (~30–50% for amebic colitis), and at least three stool specimens should be evaluated after concentration and staining. Multiple serologic assays are available; these tests are fairly sensitive, although sensitivity is lower (~70% in colitis) early in illness, and they cannot distinguish recent and old disease, as they remain positive for years after infection. Commercially available stool antigen tests (TechLab II, CELISA, QUIK CHEK) can distinguish *E histolytica* from nonpathogenic species and offer improved sensitivity (greater than 90% for colitis). The QUIK CHEK assay is FDA-approved, offers rapid point-of-care diagnosis, and is available in a combined assay for amebiasis, giardiasis, and cryptosporidiosis. Highly sensitive molecular tests are not used routinely but available in some high resource settings within commercial panels for identifying gut pathogens. Colonoscopy of uncleansed bowel typically shows no specific findings in mild intestinal disease; in severe disease, ulcers may be found with intact intervening friable mucosa, resembling inflammatory bowel disease (Figure 35–7). Examination of fresh ulcer exudate for motile trophozoites and for *E histolytica* antigen may yield a diagnosis.

2. Hepatic abscess—Serologic tests for antiamebic antibodies are almost always positive, except very early in the infection. Thus, a negative test in a suspicious case should be repeated in about a week. The TechLab II antigen test can be used to test serum with good sensitivity if used before the initiation of therapy. Examination of stools for organisms or antigen is frequently negative; the antigen test is positive in ~40% of cases. As imaging studies cannot distinguish amebic and pyogenic abscesses, when a diagnosis is not available from serologic studies, percutaneous aspiration may be indicated, ideally with an image-guided needle. Aspiration typically yields brown or yellow fluid. Detection of organisms in the aspirate is uncommon, but detection of *E histolytica* antigen is very sensitive and diagnostic. The key risk of aspiration is peritoneal spillage leading to peritonitis from amoebas or other (pyogenic or echinococcal) organisms.



▲ **Figure 35–7.** Gross pathology showing intestinal ulcers due to amebiasis. (From Dr. Mae Melvin, Public Health Image Library, CDC.)

D. Imaging

Liver abscesses can be identified by ultrasonography, CT, or MRI, typically with round or oval low-density nonhomogeneous lesions, with abrupt transition from normal liver to the lesion, and hypoechoic centers. Abscesses are most commonly single, but more than one may be present. The right lobe is usually involved.

Treatment

Treatment of amebiasis generally entails the use of metronidazole or tinidazole to eradicate tissue trophozoites and a luminal amebicide to eradicate intestinal cysts (Table 35–6). Asymptomatic infection with *E dispar* does not require therapy. This organism cannot be differentiated morphologically from *E histolytica*, but with negative serology *E dispar* colonization is likely, and treatment is not indicated. Intestinal colonization with *E histolytica* is treated with a luminal agent. Effective luminal agents are diloxanide furoate (500 mg orally three times daily with meals for 10 days), iodoquinol (diiodohydroxyquin; 650 mg orally three times daily for 21 days), and paromomycin (30-mg/kg base orally, maximum 3 g, in three divided doses after meals daily for 7 days). Side effects associated with luminal agents are flatulence with diloxanide furoate, mild diarrhea with iodoquinol, and gastrointestinal symptoms with paromomycin. Relative contraindications are thyroid disease for iodoquinol and kidney disease for iodoquinol or paromomycin.

Treatment of intestinal amebiasis requires tinidazole (2 g orally once daily for 3–5 days) or metronidazole (750 mg orally three times daily for 10 days) plus a luminal agent (Table 35–6). Tinidazole offers simpler dosing, a more rapid clinical response, and fewer side effects than metronidazole. Side effects from either agent include transient nausea, vomiting, epigastric discomfort, headache, or a metallic taste. A disulfiram-like reaction may occur if alcohol is coingested. Metronidazole and tinidazole should be avoided in pregnant or nursing mothers, if possible. Fluid and electrolyte replacement is

Table 35–6. Treatment of amebiasis.¹

Clinical Setting	Drugs of Choice and Adult Dosage	Alternative Drugs and Adult Dosage
Asymptomatic intestinal infection	Luminal agent: Diloxanide furoate, ² 500 mg orally three times daily for 10 days or– Iodoquinol, 650 mg orally three times daily for 21 days or– Paromomycin, 10 mg/kg orally three times daily for 7 days	
Mild to moderate intestinal infection	Metronidazole, 750 mg orally three times daily (or 500 mg intravenously every 6 hours) for 10 days or– Tinidazole, 2 g orally daily for 3 days plus– Luminal agent (see above)	Luminal agent (see above) plus either– Tetracycline, 250 mg orally three times daily for 10 days or– Erythromycin, 500 mg orally four times daily for 10 days
Severe intestinal infection	Metronidazole, 750 mg orally three times daily (or 500 mg intravenously every 6 hours) for 10 days or– Tinidazole, 2 g orally daily for 5 days plus– Luminal agent (see above)	Luminal agent (see above) plus either– Tetracycline, 250 mg orally three times daily for 10 days or– Dehydroemetine ² or emetine, ² 1 mg/kg subcutaneously or intramuscularly for 3–5 days
Hepatic abscess, ameboma, and other extraintestinal disease	Metronidazole, 750 mg orally three times daily (or 500 mg intravenously every 6 hours) for 10 days or– Tinidazole, 2 g orally daily for 5 days plus– Luminal agent (see above)	Dehydroemetine ² or emetine, ² 1 mg/kg subcutaneously or intramuscularly for 8–10 days, followed by (liver abscess only) chloroquine, 500 mg orally twice daily for 2 days, then 500 mg daily for 21 days plus– Luminal agent (see above)

¹See text for additional details and cautions.²Not available in the United States.

also important for patients with significant diarrhea. Surgical management of acute complications of intestinal amebiasis is best avoided whenever possible. Successful therapy of severe amebic colitis may be followed by post-dysenteric colitis, with continued diarrhea without persistent infection; this syndrome generally resolves in weeks to months.

Amebic liver abscess is also treated with metronidazole or tinidazole plus a luminal agent (even if intestinal infection is not documented; Table 35–6). Metronidazole can be used intravenously when necessary. With failure of initial response to metronidazole or tinidazole, chloroquine, emetine, or dehydroemetine may be added. Needle aspiration may be helpful for large abscesses (over 5–10 cm), in particular if the diagnosis remains uncertain, if there is an initial lack of response, or if a patient is very ill, suggesting imminent abscess rupture. With successful therapy, abscesses disappear slowly (over months).

► Prevention & Control

Prevention requires safe water supplies; sanitary disposal of human feces; adequate cooking of food; protection of food from fly contamination; hand washing; and, in endemic areas, avoidance of fruits and vegetables that cannot be cooked or peeled. Water supplies can be boiled, treated with iodine

(0.5-mL tincture of iodine per liter for 20 minutes; cysts are resistant to standard concentrations of chlorine), or filtered.

Shirley DT et al. A review of the global burden, new diagnostics, and current therapeutics for amebiasis. *Open Forum Infect Dis.* 2018;5:ofy161. [PMID: 30046644]

COCCIDIOSIS (CRYPTOSPORIDIOSIS, ISOSPORIASIS, CYCLOSPORIASIS, SARCOCYSTOSIS) & MICROSPORIDIOSIS



ESSENTIALS OF DIAGNOSIS

- Acute diarrhea, especially in children in developing countries.
- Outbreaks of diarrhea secondary to contaminated water or food.
- Prolonged diarrhea in immunocompromised persons.
- Diagnosis mostly by identifying organisms in specially stained stool specimens.

► General Considerations

The causes of coccidiosis are *Cryptosporidium* species (*C parvum*, *C hominis*, and others); *Cystoisospora* (formerly *Isospora*) *belli*; *Cyclospora cayetanensis*; and *Sarcocystis* species. Microsporidiosis is caused by at least 14 species, most commonly *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. These infections occur worldwide, particularly in the tropics and in regions where hygiene is poor. They are causes of endemic childhood gastroenteritis (particularly in malnourished children in developing countries); institutional and community outbreaks of diarrhea; traveler's diarrhea; and acute and chronic diarrhea in immunosuppressed patients, in particular those with AIDS. They are all notable for the potential to cause prolonged diarrhea, often lasting for a number of weeks. Clustering occurs in households, day care centers, and among sexual partners.

The infectious agents are oocysts (coccidiosis) or spores (microsporidiosis) transmitted from person to person or by contaminated drinking or swimming water or food. Ingested oocysts release sporozoites that invade and multiply in enterocytes, primarily in the small bowel. Coccidian oocysts and microsporidian cysts can remain viable in the environment for years.

Cryptosporidiosis is a zoonosis (*C parvum* principally infects cattle), but most human infections are acquired from humans, in particular with *C hominis*. Cryptosporidia are highly infectious and readily transmitted in day care settings and households. They have caused large community outbreaks due to contaminated water supplies (causing ~400,000 illnesses in Milwaukee in 1993 and ~2780 illnesses in Oregon in 2013) and are the leading cause of recreational water-associated outbreaks of gastroenteritis. In the developing world, cryptosporidiosis is a leading cause of childhood diarrhea. In a study of causes of moderate-to-severe diarrhea in Asia and Africa, *Cryptosporidium* was the second most commonly identified pathogen in children under 2 years of age.

C belli and *C cayetanensis* appear to infect only humans. *C cayetanensis* has caused a number of food-borne outbreaks in the United States in recent years, most commonly associated with imported fresh produce. *Sarcocystis* infects many species; humans are intermediate hosts (infected by ingestion of fecal sporocysts) for some species but definitive hosts for *Sarcocystis bovihominis* and *Sarcocystis suihominis* (infected by ingestion of tissue cysts in undercooked beef and pork, respectively).

► Clinical Findings

A. Symptoms and Signs

1. Coccidiosis—

A. CRYPTOSPORIDIOSIS—The incubation period appears to be ~14 days. In developing countries, disease is primarily in children under 5 years of age, causing 5–10% of childhood diarrhea. Presenting symptoms include acute watery diarrhea, abdominal pain, and cramps, with rapid resolution in most patients; however, symptoms quite commonly persist for 2 weeks or more. In developed countries, most patients are adults. Diarrhea in immunocompetent

individuals typically lasts from 5 to 10 days. It is usually watery, with accompanying abdominal pain and cramps, nausea, vomiting, and fever. Relapses may follow initial resolution of symptoms. Mild illness and asymptomatic infection are also common.

Cryptosporidiosis is a well-characterized cause of diarrhea in those with AIDS. It was common before the advent of highly active antiretroviral therapy, particularly with advanced immunosuppression. Clinical manifestations are variable, but patients commonly have chronic diarrhea with frequent foul-smelling stools, malabsorption, and weight loss. Severe, life-threatening watery diarrhea may be seen. Cryptosporidiosis also causes extraintestinal disease with AIDS, including pulmonary infiltrates with dyspnea and biliary tract infection with sclerosing cholangitis and AIDS cholangiopathy.

B. ISOSPORIASIS—The incubation period for *C belli* is about 1 week. In immunocompetent persons, it usually causes a self-limited watery diarrhea lasting 2–3 weeks, with abdominal cramps, anorexia, malaise, and weight loss. Fever is unusual. Chronic symptoms may persist for months. In immunocompromised patients, isosporiasis more commonly causes severe and chronic diarrhea, with complications including marked dehydration, malnutrition, and hemorrhagic colitis. Extraintestinal disease has been reported rarely.

C. CYCLOSPORIASIS—*C cayetanensis* oocysts must undergo a period of sporulation of 7 days or more after shedding before they become infectious. Therefore, person-to-person spread is unlikely, and spread has typically been due to contaminated food (especially fresh produce) and water. The incubation period is 1–11 days. Infections can be asymptomatic. Cyclosporiasis causes an illness similar to that described for the other pathogens included in this section, with watery diarrhea, abdominal cramps, nausea, fatigue, and anorexia. Fever is seen in 25% of cases. Symptoms typically continue for 2 weeks or longer and may persist for months without therapy. Relapses of diarrhea are common. Diarrhea may be preceded by a flu-like prodrome and followed by persistent fatigue. In immunocompromised patients, cyclosporiasis is typically more severe and prolonged, with chronic fulminant watery diarrhea and weight loss.

D. SARCOCYSTOSIS—*Sarcocystis* infection is common in some developing countries but is usually asymptomatic. Infection appears to most commonly follow the ingestion of undercooked beef or pork, leading to the development of cysts in muscle, with myalgias, fever, bronchospasm, pruritic rash, lymphadenopathy, and subcutaneous nodules. Ingestion of fecal sporocysts may lead to gastrointestinal symptoms.

2. Microsporidiosis—Microsporidia are obligate intracellular protozoans that cause a wide spectrum of diseases. Many infections are of zoonotic origin, but human-to-human transmission has been documented. Infection is mainly by ingestion of spores, but also by direct inoculation of the eyes. In immunocompetent hosts, microsporidian infections most commonly present as self-limited diarrhea. Ocular infections have also been described. Disease from microsporidia is seen mainly in immunocompromised

persons, particularly those with AIDS. Infections in AIDS patients are most commonly with *E. bieneusi* and *E. intestinalis*. They cause chronic diarrhea, with anorexia, bloating, weight loss, and wasting, especially in those with advanced immunodeficiency. Fever is usually not seen. Other illnesses in immunocompromised persons associated with microsporidians (including the genera *Enterocytozoon*, *Encephalitozoon*, *Brachiola*, *Vittaforma*, *Pleistophora*, *Trachipleistophora*, and *Microsporidium*) include biliary tract disease (AIDS cholangiolopathy), genitourinary infection with cystitis, kidney disease, hepatitis, peritonitis, myositis, respiratory infections including sinusitis, central nervous system infections including granulomatous encephalitis, and disseminated infections. Ocular infections with *Encephalitozoon* species cause conjunctivitis and keratitis, presenting as redness, photophobia, and loss of visual acuity.

B. Laboratory Findings

1. Coccidioides—

A. CRYPTOSPORIDIOSIS—Typically, stool is without blood or leukocytes. Diagnosis is traditionally made by detecting the organism in stool using a modified acid-fast stain; this technique is relatively insensitive, and multiple specimens should be evaluated before ruling out the diagnosis. Of note, routine evaluation for ova and parasites typically does not include a modified acid-fast stain, so this must be specifically requested in many laboratories. Various antigen detection methods, including immunofluorescence microscopy, ELISA, and immunochromatography, offer improved sensitivity and specificity, both over 90% with available assays, and these methods may be considered the optimal means of diagnosis. Molecular diagnostic panels that recognize *Cryptosporidium* and other enteropathogens in stool are available but expensive.

B. ISOSPORIASIS—Diagnosis of isosporiasis is by examination of stool wet mounts or after modified acid-fast staining, in which the organism is clearly distinguishable from other parasites. Other stains also show the organism. Shedding of oocysts may be intermittent, so the sensitivity of stool evaluation is not high, and multiple samples should be examined. The organism may also be identified in duodenal aspirates or small bowel biopsies.

C. CYCLOSPORIASIS—Diagnosis is made by examination of stool wet mounts or after modified acid-fast staining. Multiple specimens may need to be examined to make a diagnosis; concentration of specimens improves sensitivity. The organism can also be identified in small bowel aspirates or biopsy specimens. Molecular assays with high sensitivity and specificity, including multi-pathogen panels, are available.

D. SARCOCYSTOSIS—Eosinophilia and elevated creatine kinase may be seen. Diagnosis is by identification of the acid-fast organisms in stool or by identification of trophozoites or bradyzoites in tissue biopsies.

2. Microsporidiosis—Diagnosis can be made by identification of organisms in specially stained stool, fluid, or tissue specimens, for example with Weber chromotrope-based

stain. Electron microscopy is helpful for confirmation of the diagnosis and speciation. PCR and culture techniques are available but not used routinely.

► Treatment

Most acute infections with these pathogens in immunocompetent persons are self-limited and do not require treatment. Supportive treatment for severe or chronic diarrhea includes fluid and electrolyte replacement and, in some cases, parenteral nutrition.

1. Coccidioides—

A. CRYPTOSPORIDIOSIS—Treatment of cryptosporidiosis is challenging. No agent is clearly effective. Modest benefits have been seen in some (but not other) studies with paromomycin, a nonabsorbed aminoglycoside (25–35 mg/kg orally for 14 days has been used), and nitazoxanide (500 mg–1 g orally twice daily for 3 days in immunocompetent patients and 2–8 weeks in advanced AIDS patients), which is approved in the United States for this indication. Other agents that have been used with mixed success in AIDS patients with cryptosporidiosis include azithromycin, spiramycin, bovine hyperimmune colostrum, and octreotide. Reversing immunodeficiency with effective antiretroviral therapy is of greatest importance.

B. ISOSPORIASIS—Isosporiasis is effectively treated in immunocompetent and immunosuppressed persons with TMP-SMZ (160 mg/800 mg orally two to four times daily for 10 days, with the higher dosage for patients with AIDS). An alternative therapy is pyrimethamine (75 mg orally in four divided doses) with folinic acid (10–25 mg/day orally). Maintenance therapy with low-dose TMP-SMZ (160 mg/800 mg daily or three times per week) or Fansidar (1 tablet weekly) prevents relapse in those with persistent immunosuppression.

C. CYCLOSPORIASIS—Cyclosporiasis is also treated with TMP-SMZ (dosing as for isosporiasis). With AIDS, long-term maintenance therapy (160 mg/800 mg three times weekly) helps prevent relapse. For patients intolerant of TMP-SMZ, ciprofloxacin (500 mg orally twice daily for 7 days) showed efficacy, albeit with less ability to clear the organism than TMP-SMZ.

D. SARCOCYSTOSIS—For sarcocystosis, no specific treatment is established, but patients may respond to therapy with albendazole or TMP-SMZ.

2. Microsporidiosis—Treatment of microsporidiosis is complex. Infections with most species, including those causing gastrointestinal and other manifestations, should be treated with albendazole (400 mg orally twice daily for 2–4 weeks), which has activity against a number of species, but relatively poor efficacy (about 50%) against *E. bieneusi*, the most common microsporidian cause of diarrhea in AIDS patients. Fumagillin, which is used to treat honeybees and fish with microsporidian infections, has shown benefit in clinical trials at a dose of 20 mg three times per day for 14 days; treatment was accompanied by reversible thrombocytopenia. As with cryptosporidiosis, the best means of controlling microsporidiosis in AIDS patients is

to restore immune function with effective antiretroviral therapy. Ocular microsporidiosis can be treated with topical fumagillin solution (3 mg/mL); this probably should be given with concurrent systemic therapy with albendazole. Adjunctive management may include topical corticosteroids to decrease inflammation and keratoplasty.

► Prevention

Water purification is important for control of these infections. Chlorine disinfection is not effective against cryptosporidial oocysts, so other purification measures are needed. Immunocompromised patients should boil or filter drinking water and should consider avoidance of lakes and swimming pools. Routine precautions (hand washing, gloves, disinfection) should prevent institutional patient-to-patient spread. Optimal means of preventing microsporidial infections are not well understood, but water purification and body substance precautions for immunocompromised and hospitalized individuals are likely effective.

Giangaspero A et al. Human cyclosporiasis. Lancet Infect Dis. 2019;19:e226. [PMID: 30885589]

Hemphill A et al. Comparative pathobiology of the intestinal protozoan parasites *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium parvum*. Pathogens. 2019;8:E116. [PMID: 31362451]

GIARDIASIS



ESSENTIALS OF DIAGNOSIS

- ▶ Acute diarrhea may be profuse and watery.
- ▶ Chronic diarrhea with greasy, malodorous stools.
- ▶ Abdominal cramps, distention, flatulence.
- ▶ Cysts or trophozoites in stools.

► General Considerations

Giardiasis is a protozoal infection of the upper small intestine caused by the flagellate *Giardia lamblia* (also called *Giardia intestinalis* and *Giardia duodenalis*). The parasite occurs worldwide, most abundantly in areas with poor sanitation. In developing countries, young children are very commonly infected. In the United States and Europe, the infection is the most common intestinal protozoal pathogen; the US estimate is 100,000 to 2.5 million new infections leading to 5000 hospital admissions yearly. Groups at special risk include travelers to *Giardia*-endemic areas, those who swallow contaminated water during recreation or wilderness travel, men who have sex with men, and persons with impaired immunity. Outbreaks are common in households, children's day care centers, and residential facilities, and may occur as a result of contamination of water supplies.

The organism occurs in feces as a flagellated trophozoite and as a cyst. Only the cyst form is infectious by the oral

route; trophozoites are destroyed by gastric acidity. Humans are a reservoir for the pathogen; dogs, cats, beavers, and other mammals have been implicated but not confirmed as reservoirs. Under suitable moist, cool conditions, cysts can survive in the environment for weeks to months. Cysts are transmitted as a result of fecal contamination of water or food, by person-to-person contact, or by anal-oral sexual contact. The infectious dose is low, requiring as few as ten cysts. After the cysts are ingested, trophozoites emerge in the duodenum and jejunum. Epithelial damage and mucosal invasion are uncommon. Hypogammaglobulinemia, low secretory IgA levels in the gut, achlorhydria, and malnutrition favor the development of infection.

► Clinical Findings

A. Symptoms and Signs

It is estimated that about 50% of infected persons have no discernable infection, about 10% become asymptomatic cyst passers, and 25–50% develop an acute diarrheal syndrome. Acute diarrhea may clear spontaneously but is commonly followed by chronic diarrhea. The incubation period is usually 1–3 weeks but may be longer. The illness may begin gradually or suddenly. The acute phase may last days or weeks, and is usually self-limited. The initial illness may include profuse watery diarrhea, and hospitalization may be required due to dehydration, particularly in young children. Typical symptoms of chronic disease are abdominal cramps, bloating, flatulence, nausea, malaise, and anorexia. Fever and vomiting are uncommon. Diarrhea is usually not severe in the chronic stage of infection; stools are greasy or frothy and foul smelling, without blood, pus, or mucus. The diarrhea may be daily or recurrent; intervening periods may include constipation. Symptoms can persist for weeks to months. Weight loss is frequent. Chronic disease can include malabsorption, including fat and protein-losing enteropathy and vitamin deficiencies.

B. Laboratory Findings

Most patients seek medical attention after having been ill for over a week, commonly with weight loss of 5 kg or more. Stool is generally without blood or leukocytes. Diagnosis is traditionally made by the identification of trophozoites or cysts in stool. A wet mount of liquid stool may identify motile trophozoites. Stained fixed specimens may show cysts or trophozoites. Cysts may not be detected in the stool at the onset of the illness. Cyst excretion may be prolonged after the self-limited acute phase of infection. Sensitivity of stool analysis is not ideal, estimated at 50–80% for a single specimen and over 90% for three specimens. Sampling of duodenal contents with a string test or biopsy is no longer generally recommended, but biopsies may be helpful in very ill or immunocompromised patients. When giardiasis is suspected, stool antigen assays are simpler and cheaper than repeated stool examinations, but these tests will not identify other stool pathogens. Multiple tests, which identify antigens of trophozoites or cysts in stool, are available. They are generally quite sensitive (85–98%) and specific (90–100%). Molecular diagnostic

panels that recognize *Giardia* and other enteropathogens in stool are available but expensive.

► Treatment

The treatments of choice for giardiasis are tinidazole (2 g orally once) or metronidazole (250 mg orally three times daily for 5–7 days). The drugs are not universally effective; cure rates for single courses are typically about 80–95%. Toxicities are as described for treatment of amebiasis, but the lower dosages used for giardiasis limit side effects. Albendazole (400 mg orally once daily for 5 days) and nitazoxanide (500 mg orally twice daily for 3 days) both appear to have similar efficacy and fewer side effects compared with metronidazole, although data are limited, and a 2016 meta-analysis suggested superiority in efficacy of tinidazole over albendazole. Nitazoxanide is generally well tolerated but may cause mild gastrointestinal side effects. Other drugs with activity against *Giardia* include furazolidone (100 mg orally four times a day for 7 days), which is about as effective as the other named drugs but causes gastrointestinal side effects, and paromomycin (500 mg orally three times a day for 7 days), which appears to have somewhat lower efficacy but, unlike metronidazole, tinidazole, and furazolidone, is safe in pregnancy. Symptomatic giardiasis should always be treated. Treatment of asymptomatic patients should be considered, since they can transmit the infection. With a suggestive presentation but negative diagnostic studies, an empiric course of treatment may be appropriate. Household or day care contacts with an index case should be tested and treated if infected.

► Prevention

Community chlorination (0.4 mg/L) of water is relatively ineffective for inactivating cysts, so filtration is required. For wilderness or international travelers, bringing water to a boil for 1 minute or filtration with a pore size less than 1 mcm are adequate. In day care centers, appropriate disposal of diapers and frequent hand washing are essential.

Mmbaga BT et al. *Cryptosporidium* and *Giardia* infections in children: a review. *Pediatr Clin North Am.* 2017;64:837. [PMID: 28734513]

TRICHOMONIASIS



ESSENTIALS OF DIAGNOSIS

- Women: copious vaginal discharge.
- Men: nongonococcal urethritis.
- Motile trichomonads on wet mounts.

► General Considerations

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis* and is among the most common sexually

transmitted diseases, causing vaginitis in women and nongonococcal urethritis in men. It can also occasionally be acquired by other means, since it can survive in moist environments for several hours.

► Clinical Findings

A. Symptoms and Signs

T vaginalis is often harbored asymptotically. For women with symptomatic disease, after an incubation period of 5 days to 4 weeks, a vaginal discharge develops, often with vulvovaginal discomfort, pruritus, dysuria, dyspareunia, or abdominal pain. Examination shows a copious discharge, which is usually not foul smelling but is often frothy and yellow or green in color. Inflammation of the vaginal walls and cervix with punctate hemorrhages are common. Most men infected with *T vaginalis* are asymptomatic, but it can be isolated from about 10% of men with nongonococcal urethritis. In men with trichomonal urethritis, the urethral discharge is generally more scanty than with other causes of urethritis.

B. Diagnostic Testing

Diagnosis is traditionally made by identifying the organism in vaginal or urethral secretions. Examination of wet mounts will show motile organisms. Tests for bacterial vaginosis ($\text{pH} > 4.5$, fishy odor after addition of potassium hydroxide) are often positive with trichomoniasis. Newer point-of-care antigen detection and nucleic acid probe hybridization tests and nucleic acid amplification assays offer improved sensitivity compared to wet mount microscopy and excellent specificity.

► Treatment

The treatment of choice is tinidazole or metronidazole, each as a 2 g single oral dose. Tinidazole may be better tolerated and active against some resistant parasites. Toxicities of these drugs are discussed in the section on amebiasis. If the large single dose cannot be tolerated, an alternative metronidazole dosage is 500 mg orally twice daily for 1 week. A meta-analysis suggested that a 7-day course of metronidazole (500 mg twice daily) is more effective than a single dose; this regimen is recommended for HIV-infected women and may become standard for other groups. All infected persons should be treated, even if asymptomatic, to prevent subsequent symptomatic disease and limit spread. Treatment failure suggests reinfection, but metronidazole-resistant organisms have been reported. These may be treated with tinidazole, longer courses of metronidazole, intravaginal paromomycin, or other experimental therapies (see Chapter 18).

Van Gerwen OT et al. Recent advances in the epidemiology, diagnosis, and management of *Trichomonas vaginalis* infection. *F1000Res.* 2019;8:1666. [PMID: 31583080]

HELMINTHIC INFECTIONS

TREMATODE (FLUKE) INFECTIONS

SCHISTOSOMIASIS (Bilharziasis)



ESSENTIALS OF DIAGNOSIS

- ▶ History of freshwater exposure in an endemic area.
- ▶ **Acute schistosomiasis:** fever, headache, myalgias, cough, urticaria, diarrhea, and eosinophilia.
- ▶ **Intestinal schistosomiasis:** abdominal pain, diarrhea, and hepatomegaly, progressing to anorexia, weight loss, and features of portal hypertension.
- ▶ **Urinary schistosomiasis:** hematuria and dysuria, progressing to hydronephrosis and urinary infections.
- ▶ **Diagnosis:** characteristic eggs in feces or urine; biopsy of rectal or bladder mucosa; positive serology.

General Considerations

Schistosomiasis, which affects more than 200 million persons worldwide, leads to severe consequences in 20 million persons and about 100,000 deaths annually. The disease is caused by six species of trematode blood flukes. Five species cause intestinal schistosomiasis, with infection of mesenteric venules: *Schistosoma mansoni*, which is present in Africa, the Arabian peninsula, South America, and the Caribbean; *Schistosoma japonicum*, which is endemic in China and Southeast Asia; *Schistosoma mekongi*, which is endemic near the Mekong River in Southeast Asia; and *Schistosoma intercalatum* and *Schistosoma guineensis*, which occur in parts of Africa. *Schistosoma haematobium* causes urinary schistosomiasis, with infection of venules of the urinary tract, and is endemic in Africa and the Middle East. Transmission of schistosomiasis is focal, with greatest prevalence in poor rural areas. Control efforts have diminished transmission significantly in many areas, but high-level transmission remains common in sub-Saharan Africa and some other areas. Prevalence of infection and illness typically peaks at about 15–20 years of age.

Humans are infected with schistosomes after contact with freshwater containing cercariae released by infected snails. Infection is initiated by penetration of skin or mucous membranes. After penetration, schistosomulae migrate to the portal circulation, where they rapidly mature. After about 6 weeks, adult worms mate, and migrate to terminal mesenteric or bladder venules, where females deposit their eggs. Some eggs reach the lumen of the bowel or bladder and are passed with feces or urine, while others are retained in the bowel or bladder wall or transported in the circulation to other tissues, in particular the liver. Disease in endemic areas is primarily due to a host response to eggs, with granuloma formation and

inflammation, eventually leading to fibrosis. Chronic infection can result in scarring of mesenteric or vesicular blood vessels, leading to portal hypertension and alterations in the urinary tract. In previously uninfected individuals, such as travelers with freshwater contact in endemic regions, acute schistosomiasis may occur, with a febrile illness 2–8 weeks after infection.

Clinical Findings

A. Symptoms and Signs

1. Cercarial dermatitis—Following cercarial penetration, localized erythema develops in some individuals, which can progress to a localized pruritic maculopapular rash that persists for some days. Dermatitis can be caused by human schistosomes and, in nontropical areas, by bird schistosomes that cannot complete their life cycle in humans (swimmer's itch).

2. Acute schistosomiasis (Katayama syndrome)—A febrile illness may develop 2–8 weeks after exposure in persons without prior infection, most commonly after heavy infection with *S. mansoni* or *S. japonicum*. Presenting symptoms and signs include acute onset of fever; headache; myalgias; cough; malaise; urticaria; diarrhea, which may be bloody; hepatosplenomegaly; lymphadenopathy; and pulmonary infiltrates. Localized lesions may occasionally cause severe manifestations, including CNS abnormalities and death. Acute schistosomiasis usually resolves in 2–8 weeks.

3. Chronic schistosomiasis—Many infected persons have light infections and are asymptomatic, but an estimated 50–60% have symptoms and 5–10% have advanced organ damage. Asymptomatic infected children may suffer from anemia and growth retardation. Symptomatic patients with intestinal schistosomiasis typically experience abdominal pain, fatigue, diarrhea, and hepatomegaly. Over years, anorexia, weight loss, weakness, colonic polyps, and features of portal hypertension develop. Late manifestations include hematemesis from esophageal varices, hepatic failure, and pulmonary hypertension. Urinary schistosomiasis may present within months of infection with hematuria and dysuria, most commonly in children and young adults. Fibrotic changes in the urinary tract can lead to hydroureter, hydronephrosis, bacterial urinary infections and, ultimately, kidney disease or bladder cancer.

B. Laboratory Findings

Microscopic examination of stool or urine for eggs, evaluation of tissue, or serologic tests establish the diagnosis. Characteristic eggs can be identified on smears of stool or urine. The most widely used stool test is the Kato-Katz technique. Quantitative tests that yield more than 400 eggs per gram of feces or 10 mL of urine are indicative of heavy infections with increased risk of complications. Diagnosis can also be made by biopsy of the rectum, colon, liver, or bladder. Serologic tests include an ELISA available from the CDC that is 99% specific for all species, but cannot distinguish acute and past infection. Sensitivity of the test is 99% for *S. mansoni*, 95% for *S. haematobium*, but less than

50% for *S japonicum*. Serology is of limited use in endemic settings but can be helpful in travelers from nonendemic regions. The most widely used point-of-care assays target circulating anodic and cathodic antigens to detect circulating schistosome antigens in serum and urine. Antigen tests have better sensitivity than stool smears, especially for *S mansoni*; sensitivity is lower for *S haematobium*. Molecular tests for schistosomiasis have been developed but are not routinely used for diagnosis. In acute schistosomiasis, leukocytosis and marked eosinophilia may occur; serologic tests may become positive before eggs are seen in stool or urine. After therapy, eggs may be shed in stool or urine for months, and so the identification of eggs in fluids or tissue cannot distinguish past or active disease. With a diagnosis of schistosomiasis, evaluation for the extent of disease is warranted, including liver function studies and imaging of the liver with intestinal disease and ultrasound or other imaging studies of the urinary system in urinary disease.

► Treatment

Treatment is indicated for all schistosome infections. In areas where recurrent infection is common, treatment is valuable in reducing worm burdens and limiting clinical complications. The drug of choice for schistosomiasis is praziquantel. The drug is administered for 1 day at an oral dose of 40 mg/kg (in one or two doses) for *S mansoni*, *S haematobium*, *S intercalatum*, and *S guineensis* infections and a dose of 60 mg/kg (in two or three doses) for *S japonicum* and *S mekongi*. Cure rates are generally greater than 80% after a single treatment, and those not cured have marked reduction in the intensity of infection. Praziquantel is active against invading cercariae but not developing schistosomulae. Therefore, the drug may not prevent illness when given after exposure and, for recent infections, a repeat course after a few weeks may be appropriate. Praziquantel may be used during pregnancy. Resistance to praziquantel has been reported. Toxicities include abdominal pain, diarrhea, urticaria, headache, nausea, vomiting, and fever, and may be due both to direct effects of the drug and responses to dying worms. Alternative therapies are oxamniquine for *S mansoni* infection and metrifonate for *S haematobium* infection. Both of these drugs currently have limited availability (they are not available in the United States), and resistance may be a problem. No second-line drug is available for *S japonicum* infections. The antimalarial drug artemether has activity against schistosomulae and adult worms and may be effective in chemoprophylaxis; however, it is expensive, and long-term use in malarious areas might select for resistant malaria parasites. With severe disease, use of corticosteroids in conjunction with praziquantel may decrease complications. Treatment should be followed by repeat examinations for eggs about every 3 months for 1 year after therapy, with re-treatment if eggs are seen.

► Prevention

Travelers to endemic areas should avoid freshwater exposure. Vigorous toweling after exposure may limit cercarial penetration. Chemoprophylaxis with artemether has

shown efficacy but is not standard practice. Community control of schistosomiasis includes improved sanitation and water supplies, elimination of snail habitats, and intermittent treatment to limit worm burdens.

Nelwan ML. Schistosomiasis: life cycle, diagnosis, and control. Curr Ther Res Clin Exp. 2019;91:5. [PMID: 31372189]

LIVER, LUNG, & INTESTINAL FLUKES

CLONORCHIASIS & OPISTHORCHIASIS

Infection by *Clonorchis sinensis*, the Chinese liver fluke, is endemic in areas of Japan, Korea, China, Taiwan, Southeast Asia, and the far eastern part of Russia. An estimated 15 million people are infected (13 million in China); in some communities, prevalence can reach 80%. Opisthorchiasis is principally caused by *Opisthorchis felineus* (regions of the former Soviet Union) or *Opisthorchis viverrini* (Thailand, Laos, Vietnam). Clonorchiiasis and opisthorchiiasis are clinically indistinguishable. Parasite eggs are shed into water in human or animal feces, where they infect snails, which release cercariae, which infect fish. Human infection follows ingestion of raw, undercooked, or pickled freshwater fish containing metacercariae. These parasites excyst in the duodenum and ascend into the biliary tract, where they mature and remain for many years, shedding eggs in the bile.

Most patients harbor few parasites and are asymptomatic. An acute illness can occur 2–3 weeks after initial infection, with fever, malaise, abdominal pain, anorexia, tender hepatomegaly, urticaria, and eosinophilia. The acute syndrome is difficult to diagnose, since ova may not appear in the feces until 3–4 weeks after onset of symptoms. In chronic heavy infections, findings include abdominal pain, anorexia, weight loss, and tender hepatomegaly. More serious findings can include recurrent bacterial cholangitis and sepsis, cholecystitis, liver abscess, and pancreatitis. An increased risk of cholangiocarcinoma has been documented.

Early diagnosis is presumptive, based on clinical findings and epidemiology. Subsequent diagnosis is made by finding characteristic eggs in stool or duodenal or biliary contents. The stool Kato-Katz test is widely used; performing repeated tests improves sensitivity. Imaging studies show characteristic biliary tract dilatations with filling defects due to flukes. Serologic assays for clonorchiiasis with excellent sensitivity are available but cannot distinguish between past and current infection. Molecular tests have been developed but are not widely used.

The drug of choice is praziquantel, 25 mg/kg orally three times daily for 2 days, which provides cure rates over 90% and egg reduction rates of nearly 100%. One day of treatment may be sufficient. Re-treatment may be required, especially in some areas with known decreased praziquantel efficacy. The second-line drug is albendazole (400 mg orally twice daily for 7 days), which appears to be somewhat less effective. Tribendimidine, which is approved in China, has shown efficacy for clonorchiiasis similar to that of praziquantel.

PARAGONIMIASIS

Eight species of *Paragonimus* lung flukes cause human disease. The most important is *Paragonimus westermani*. *Paragonimus* species are endemic in East Asia, Oceania, West Africa, and South America, where millions of persons are infected; rare infections caused by *Paragonimus kellicotti* have occurred in North America. Eggs are released into freshwater, where parasites infect snails, and then cercariae infect crabs and crayfish. Human infection follows consumption of raw, undercooked, or pickled freshwater shellfish. Metacercariae then excyst, penetrate into the peritoneum, and pass into the lungs, where they mature into adult worms over about 2 months.

Most persons have moderate worm burdens and are asymptomatic. In symptomatic cases, abdominal pain and diarrhea develop 2 days to 2 weeks after infection, followed by fever, cough, chest pain, urticaria, and eosinophilia. Acute symptoms may last for several weeks. Chronic infection can cause cough productive of brown sputum, hemoptysis, dyspnea, and chest pain, with progression to chronic bronchitis, bronchiectasis, bronchopneumonia, lung abscess, and pleural disease. Ectopic infections can cause disease in other organs, most commonly the CNS, where disease can present with seizures, headaches, and focal neurologic findings due to parasite meningitis and to intracerebral lesions.

The diagnosis of paragonimiasis is made by identifying characteristic eggs in sputum or stool or identifying worms in biopsied tissue. Multiple examinations and concentration techniques may be needed. Serologic tests may be helpful; an ELISA available from the CDC has sensitivity and specificity more than 95%. Chest radiographs may show varied abnormalities of the lungs or pleura, including infiltrates, nodules, cavities, and fibrosis, and the findings can be confused with those of tuberculosis. With CNS disease, skull radiographs can show clusters of calcified cysts, and CT or MRI can show clusters of ring-enhancing lesions.

Treatment is with praziquantel (25 mg/kg orally three times daily for 2 days), which provides efficacy of at least 90%. Alternative therapies are bithionol and triclabendazole. As with cysticercosis, for cerebral paragonimiasis, praziquantel should generally be used with corticosteroids. Chronic infection may lead to permanent lung dysfunction and pleural disease requiring drainage procedures.

INTESTINAL FLUKES

The large intestinal fluke, *Fasciolopsis buski*, is a common parasite of pigs and humans in eastern and southern Asia. Eggs shed in stools hatch in freshwater, followed by infection of snails, and release of cercariae that encyst on aquatic plants. Humans are infected by eating uncooked plants, including water chestnuts, bamboo shoots, and watercress. Adult flukes mature in about 3 months and live in the small intestine attached to the mucosa, leading to local inflammation and ulceration. Other intestinal flukes that cause similar syndromes include *Heterophyes* (North Africa and Turkey) and *Metagonimus* (East Asia) species; these species are transmitted by undercooked freshwater fish.

Infections with intestinal flukes are often asymptomatic, although eosinophilia may be marked. In symptomatic

cases, after an incubation period of 1–2 months, manifestations include epigastric pain and diarrhea. Other gastrointestinal symptoms, ileus, edema, and ascites may be seen uncommonly. Diagnosis is based on identification of characteristic eggs or adult flukes in the stool. In contrast to other fluke infections, illness more than 6 months after travel in an endemic area is unlikely. The drug of choice is praziquantel, 25 mg/kg orally as a single dose. Alternative therapies are triclabendazole and niclosamide (for most species).

Mas-Coma S et al. Fascioliasis. Adv Exp Med Biol. 2019;1154:71.
[PMID: 31297760]

Na BK et al. Clonorchis sinensis and clonorchiasis. Acta Trop. 2019;105309. [PMID: 31862466]

CESTODE INFECTIONS

NONINVASIVE CESTODE INFECTIONS

The four major tapeworms that cause noninvasive infections in humans are the beef tapeworm *Taenia saginata*, the pork tapeworm *Taenia solium*, the fish tapeworm *Diphyllobothrium latum*, each of which can reach many meters in length, and the dwarf tapeworm *Hymenolepis nana*. *Taenia* and *Hymenolepis* species are broadly distributed, especially in the tropics; *D. latum* is most prevalent in temperate regions. Other tapeworms that can cause noninvasive human disease include the rodent tapeworm *Hymenolepis diminuta*, the dog tapeworm *Dipylidium caninum*, and other *Taenia* and *Diphyllobothrium* species. Invasive tape-worm infections, including *T. solium* (when infective eggs, rather than cysticerci are ingested) and *Echinococcus* species, will be discussed separately.

1. Beef Tapeworm

Infection is most common in cattle breeding areas. Humans are the definitive host. Gravid segments of *T. saginata* are passed in human feces to soil, where they are ingested by grazing animals, especially cattle. The eggs then hatch to release embryos that encyst in muscle as cysticerci. Humans are infected by eating raw or undercooked infected beef. Most individuals infected with *T. saginata* are asymptomatic, but abdominal pain and other gastrointestinal symptoms may be present. Eosinophilia is common. The most common presenting finding is the passage of proglottids in the stool.

2. Pork Tapeworm

T. solium is transmitted to pigs that ingest human feces. Humans can be either the definitive host (after consuming undercooked pork, leading to tapeworm infection) or the intermediate host (after consuming food contaminated with human feces containing *T. solium* eggs, leading to cysticercosis, which is discussed under Invasive Cestode Infections). As with the beef tapeworm, infection with *T. solium* adult worms is generally asymptomatic, but gastrointestinal symptoms may occur. Infection is generally recognized after passage of proglottids. Autoinfection with eggs can progress to cysticercosis.

3. Fish Tapeworm

Infection with *D. latum* follows ingestion of undercooked freshwater fish, most commonly in temperate regions. Eggs from human feces are taken up by crustaceans, these are eaten by fish, which are then infectious to humans. Infection with multiple worms over many years can occur. Infections are most commonly asymptomatic, but nonspecific gastrointestinal symptoms, including diarrhea, may occur. Diagnosis usually follows passage of proglottids. Prolonged heavy infection can lead to megaloblastic anemia and neuropathy from vitamin B₁₂ deficiency, which is due to infection-induced dissociation of the vitamin from intrinsic factor and to utilization of the vitamin by worms.

4. Dwarf Tapeworm

H. nana is the only tapeworm that can be transmitted between humans. Infections are common in warm areas, especially with poor hygiene and institutionalized populations. Infection follows ingestion of food contaminated with human feces. Eggs hatch in the intestines, where oncospheres penetrate the mucosa, encyst as cysticercoid larvae, and then rupture after about 4 days to release adult worms. Autoinfection can lead to amplification of infection. Infection with *H. nana*, the related rodent tapeworm *H. diminuta*, or the dog tapeworm *D. caninum* can also follow accidental ingestion of infected insects. *H. nana* are dwarf in size relative to other tapeworms but can reach 5 cm in length. Heavy infection is common, especially in children, and can be accompanied by abdominal discomfort, anorexia, and diarrhea.

Laboratory Findings

Diagnosis is usually made based on the identification of characteristic eggs or proglottids in stool. Egg release may be irregular, so examination of multiple specimens or concentration techniques may be needed.

Treatment

The treatment of choice for noninvasive tapeworm infections is praziquantel. A single dose of praziquantel (5–10 mg/kg orally) is highly effective, except for *H. nana*, for which the dosage is 25 mg/kg. Treatment of *H. nana* is more difficult, as the drug is not effective against maturing cysts. Therefore, a repeat treatment after 1 week and screening after therapy to document cure are appropriate with heavy infections. Therapy can be accompanied by headache, malaise, dizziness, abdominal pain, and nausea.

The alternative therapy for these infections is niclosamide. A single dose of niclosamide (2 g chewed) is effective against *D. latum*, *Taenia*, and *D. caninum* infections. For *H. nana*, therapy is continued daily for 1 week. Niclosamide may cause nausea, malaise, and abdominal pain.

Craig P et al. Intestinal cestodes. Curr Opin Infect Dis. 2007;20:524. [PMID: 17762788]

Panti-May JA et al. Worldwide overview of human infections with *Hymenolepis diminuta*. Parasitol Res. 2020;119:1997. [PMID: 32211990]

INVASIVE CESTODE INFECTIONS

1. Cysticercosis



ESSENTIALS OF DIAGNOSIS

- Exposure to *T solium* through fecal contamination of food.
- Focal CNS lesions; seizures, headache.
- Brain imaging shows cysts; positive serologic tests.

General Considerations

Cysticercosis is due to tissue infection with cysts of *T. solium* that develop after humans ingest food contaminated with eggs from human feces, thus acting as an intermediate host for the parasite. Prevalence is high where the parasite is endemic, in particular Mexico, Central and South America, the Philippines, and Southeast Asia. An estimated 20 million persons are infected with cysticerci yearly, leading to about 400,000 persons with neurologic symptoms and 50,000 deaths. Antibody prevalence rates up to 10% are recognized in some endemic areas, and the infection is one of the most important causes of seizures in the developing world and in immigrants to the United States from endemic countries. In Latin America, it is estimated that 0.5–1.5 million people suffer from epilepsy secondary to cysticercosis.

Clinical Findings

A. Symptoms and Signs

Neurocysticercosis can cause intracerebral, subarachnoid, and spinal cord lesions and intraventricular cysts. Single or multiple lesions may be present. Lesions may persist for years before symptoms develop, generally due to local inflammation or ventricular obstruction. Presenting symptoms include seizures, focal neurologic deficits, altered cognition, and psychiatric disease. Symptoms develop more quickly with intraventricular cysts, with findings of hydrocephalus and meningeal irritation, including severe headache, vomiting, papilledema, and visual loss. A particularly aggressive form of the disease, racemose cysticercosis, involves proliferation of cysts at the base of the brain, leading to alterations of consciousness and death. Spinal cord lesions can present with progressive focal findings.

Cysticercosis of other organ systems is usually clinically benign. Involvement of muscles can uncommonly cause discomfort and is identified by radiographs of muscle showing multiple calcified lesions. Subcutaneous involvement presents with multiple painless palpable skin lesions. Involvement of the eyes can present with ptosis due to extraocular muscle involvement or intraocular abnormalities.

B. Laboratory Findings and Imaging

Diagnosis generally requires consideration of both laboratory and imaging findings. The updated Del Brutto diagnostic criteria, which include laboratory and imaging findings, have demonstrated good sensitivity and specificity.

CSF examination may show lymphocytic or eosinophilic pleocytosis, decreased glucose, and elevated protein. Serology plays an important role in diagnosis; both antibody and antigen detection assays are available. ELISAs and related immunoblot assays have excellent sensitivity and specificity, but sensitivity is lower with only single or calcified lesions.

With neuroimaging by CT or MRI, multiple parenchymal cysts are most typically seen. Parenchymal calcification is also common. Performing both CT and MRI is ideal because CT is better for identification of calcification and MRI for smaller and ventricular lesions. Typical findings can be highly suggestive of the diagnosis.

Treatment

The medical management of neurocysticercosis has been controversial because the benefits of cyst clearance must be weighed against potential harm of an inflammatory response to dying worms. Antihelminthic therapy hastens radiologic improvement in parenchymal cysticercosis, but some randomized trials have shown that corticosteroids alone are as effective as specific therapy plus corticosteroids for controlling seizures. Overall, most authorities recommend treatment of active lesions, in particular lesions with a high likelihood of progression, such as intraventricular cysts. At the other end of the spectrum, inactive calcified lesions probably do not benefit from therapy. In addition, cysticidal therapy should be avoided if there is a high risk of hydrocephalus, as with subarachnoid involvement. When treatment is deemed appropriate, standard therapy consists of albendazole (10–15 mg/kg/day orally for 8 days) or praziquantel (50 mg/kg/day orally for 15–30 days). Albendazole is probably preferred, since it has shown better efficacy in some comparisons and since corticosteroids appear to lower circulating praziquantel levels but increase albendazole levels. Increasing the dosage of albendazole to 30 mg/kg/day orally may improve outcomes. Combining albendazole plus praziquantel improved outcomes compared to albendazole alone in patients with multiple viable intraparenchymal cysts. Corticosteroids are usually administered concurrently, but dosing is not standardized. Patients should be observed for evidence of localized inflammatory responses. Anticonvulsant therapy should be provided if needed, and shunting performed if required for elevated intracranial pressure. Surgical removal of cysts may be helpful for some difficult cases of neurocysticercosis and for symptomatic non-neurologic disease.

Garcia HH et al; Cysticercosis Working Group in Peru. Laboratory diagnosis of neurocysticercosis (*Taenia solium*). *J Clin Microbiol*. 2018;56:e00424-18. [PMID: 29875195]

Garcia HH et al. *Taenia solium* cysticercosis and its impact in neurological disease. *Clin Microbiol Rev*. 2020;33:e00085-19. [PMID: 32461308]

White AC et al. Diagnosis and treatment of neurocysticercosis: 2017 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Am J Trop Med Hyg*. 2018;98:945. [PMID: 29644966]

2. Echinococcosis



ESSENTIALS OF DIAGNOSIS

- ▶ History of exposure to dogs or wild canines in an endemic area.
- ▶ Large cystic lesions, most commonly of the liver or lung.
- ▶ Positive serologic tests.

General Considerations

Echinococcosis occurs when humans are intermediate hosts for canine tapeworms. Infection is acquired by ingesting food contaminated with canine feces containing parasite eggs. The principal species that infect humans are *Echinococcus granulosus*, which causes cystic hydatid disease, and *Echinococcus multilocularis*, which causes alveolar hydatid disease. *E granulosus* is transmitted by domestic dogs in areas with livestock (sheep, goats, camels, and horses) as intermediate hosts, including Africa, the Middle East, southern Europe, South America, Central Asia, Australia, New Zealand, and the southwestern United States. *E multilocularis*, which much less commonly causes human disease, is transmitted by wild canines and is endemic in northern forest areas of the Northern Hemisphere, including central Europe, Siberia, northern Japan, northwestern Canada, and western Alaska. An increase in the fox population in Europe has been associated with an increase in human cases. The disease range has also extended southward in Central Asia and China. Other species that cause limited disease in humans are endemic in South America and China.

After humans ingest parasite eggs, the eggs hatch in the intestines to form oncospheres, which penetrate the mucosa, enter the circulation, and encyst in specific organs as hydatid cysts. *E granulosus* forms cysts most commonly in the liver (65%) and lungs (25%), but the cysts may develop in any organ, including the brain, bones, skeletal muscles, kidneys, and spleen. Cysts are most commonly single. The cysts can persist and slowly grow for many years.

Clinical Findings

A. Symptoms and Signs

Infections are commonly asymptomatic and may be noted incidentally on imaging studies or present with symptoms caused by an enlarging or superinfected mass. Findings may include abdominal or chest pain, biliary obstruction, cholangitis, portal hypertension, cirrhosis, bronchial

obstruction leading to segmental lung collapse, and abscesses. Cyst leakage or rupture may be accompanied by a severe allergic reaction, including fever and hypotension. Seeding of cysts after rupture may extend the infection to new areas.

E multilocularis generally causes a more aggressive disease than *E granulosus*, with initial infection of the liver, but then local and distant spread commonly suggesting a malignancy. Symptoms based on the areas of involvement gradually worsen over years, with the development of obstructive findings in the liver and elsewhere.

B. Laboratory Findings

Serologic tests, including ELISA and immunoblot, offer sensitivity and specificity over 80% for *E granulosus* liver infections, but lower sensitivity for involvement of other organs. Serology is somewhat more reliable for *E multilocularis* infections. Serologic tests may also distinguish the two major echinococcal infections.

C. Imaging

Diagnosis is usually based on imaging studies, including ultrasonography, CT, and MRI. In *E granulosus* infection, a large cyst containing multiple daughter cysts that fill the cyst interior is highly suggestive of the diagnosis. In *E multilocularis* infection, imaging shows an irregular mass, often with areas of calcification.

Treatment

The treatment of cystic hydatid disease is with albendazole, often with cautious surgical resection of cysts. When used alone, as in cases where surgery is not possible, albendazole (10–15 mg/kg/day orally) has demonstrated efficacy, with courses of 3 months or longer duration; alternating cycles of treatment and rest may be needed. Mebendazole (40–50 mg/kg/day orally) is an alternative drug, and praziquantel may also be effective. In some cases, medical therapy is begun, with surgery performed if disease persists after some months of therapy. Another approach, in particular with inoperable cysts, is percutaneous aspiration, injection, and reaspiration (PAIR). In this approach (which should not be used if cysts communicate with the biliary tract), patients receive antihelminthic therapy, and the cyst is partially aspirated. After diagnostic confirmation by examination for parasite protoscolices, a scolicidal agent (95% ethanol, hypertonic saline, or 0.5% cetrimide) is injected, and the cyst is reaspirated after about 15 minutes. PAIR includes a small risk of anaphylaxis, which has been reported in about 2% of procedures, but death due to anaphylaxis has been rare. Treatment of alveolar cyst disease is challenging, generally relying on wide surgical resection of lesions. Therapy with albendazole before or during surgery may be beneficial and may also provide improvement or even cure in inoperable cases.

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Wen H et al. Echinococcosis: advances in the 21st century. *Clin Microbiol Rev.* 2019;32:e00075-18. [PMID: 30760475]

INTESTINAL NEMATODE (Roundworm) INFECTIONS

ASCARIASIS



ESSENTIALS OF DIAGNOSIS

- ▶ Transient cough, urticaria, pulmonary infiltrates, eosinophilia.
- ▶ Nonspecific abdominal symptoms.
- ▶ Eggs in stool; adult worms occasionally passed.

General Considerations

Ascaris lumbricoides is the most common of the intestinal helminths, causing about 800 million infections, 12 million acute cases, and 10,000 or more deaths annually. Prevalence is high wherever there is poor hygiene and sanitation or where human feces are used as fertilizer. Heavy infections are most common in children.

Infection follows ingestion of eggs in contaminated food. Larvae hatch in the small intestine, penetrate into the bloodstream, migrate to the lungs, and then travel via airways back to the gastrointestinal tract, where they develop to adult worms, which can be up to 40 cm in length, and live for 1–2 years.

Clinical Findings

Most persons with *Ascaris* infection are asymptomatic. In a small proportion of patients, symptoms develop during migration of worms through the lungs, with fever, nonproductive cough, chest pain, dyspnea, and eosinophilia, occasionally with eosinophilic pneumonia. Rarely, larvae lodge ectopically in the brain, kidney, eye, spinal cord, and other sites and may cause local symptoms.

Light intestinal infections usually produce no symptoms. With heavy infection, abdominal discomfort may be seen. Adult worms may also migrate and be coughed up, be vomited, or may emerge through the nose or anus. They may also migrate into the common bile duct, pancreatic duct, appendix, and other sites, which may lead to cholangitis, cholecystitis, pyogenic liver abscess, pancreatitis, obstructive jaundice, or appendicitis. With very heavy infestations, masses of worms may cause intestinal obstruction, volvulus, intussusception, or death. Although severe manifestations of infection are uncommon, the very high prevalence of ascariasis leads to large numbers of individuals, especially children, with important sequelae. Moderate to high worm loads in children are also associated with nutritional abnormalities due to decreased appetite and food intake, and also decreased absorption of nutrients.

The diagnosis of ascariasis is made after adult worms emerge from the mouth, nose, or anus, or by identifying characteristic eggs in the feces, usually with the Kato-Katz technique. Imaging studies demonstrate worms, with filling defects in contrast studies and at times evidence of

intestinal or biliary obstruction. Eosinophilia is marked during worm migration but may be absent during intestinal infection.

► Treatment

All infections should ideally be treated. Treatments of choice are albendazole (single 400-mg oral dose), mebendazole (single 500-mg oral dose or 100 mg twice daily for 3 days), or pyrantel pamoate (single 11-mg/kg oral dose, maximum 1 g). These drugs are all well tolerated but may cause mild gastrointestinal toxicity. They are considered safe for children above 1 year of age and in pregnancy, although use in the first trimester is best avoided. An alternative is ivermectin (single 200 mcg/kg oral dose). In endemic areas, reinfection after treatment is common. Intestinal obstruction usually responds to conservative management and antihelminthic therapy. Surgery may be required for appendicitis and other gastrointestinal complications.

TRICHURIASIS

Trichuris trichiura, the whipworm, infects about 500 million persons throughout the world, particularly in humid tropical and subtropical environments. Infection is heaviest and most frequent in children. Infections are acquired by ingestion of eggs. The larvae hatch in the small intestine and mature in the large bowel to adult worms of about 4 cm in length. The worms do not migrate through tissues.

Most infected persons are asymptomatic. Heavy infections may be accompanied by abdominal cramps, tenesmus, diarrhea, distention, nausea, and vomiting. The *Trichuris* dysentery syndrome may develop, particularly in malnourished young children, with findings resembling inflammatory bowel disease including bloody diarrhea and rectal prolapse.

Trichuriasis is diagnosed by identification of characteristic eggs and sometimes adult worms in stools. Eosinophilia is common. Treatment is typically with albendazole (400 mg/day orally) or mebendazole (200 mg/day orally), for 1–3 days for light infections or 3–7 days for heavy infections, but cure rates are lower than for ascariasis or hookworm infection. An alternative is ivermectin (200 mcg/kg orally once daily for 3 days). Oxantel pamoate (one dose of 15–30 mg/kg) has shown good efficacy in clearing infections; randomized trials showed albendazole plus oxantel pamoate (31% cure; 96% egg reduction) to be superior to mebendazole, and albendazole plus oxantel pamoate (69% cure; 99% egg reduction) and albendazole plus ivermectin (28% cure; 95% egg reduction) to be superior to albendazole plus mebendazole. Oxantel pamoate has low efficacy against *Ascaris* and hookworm infection.

HOOKWORM DISEASE



ESSENTIALS OF DIAGNOSIS

- Transient pruritic skin rash and lung symptoms.
- Anorexia, diarrhea, abdominal discomfort.

- Iron deficiency anemia.
- Characteristic eggs and occult blood in the stool.

► General Considerations

Infection with the hookworms *Ancylostoma duodenale* and *Necator americanus* is very common, especially in most tropical and subtropical regions. Both worms are broadly distributed. Prevalence is estimated at about 500 million, causing approximately 65,000 deaths each year. When eggs are deposited on warm moist soil, they hatch, releasing larvae that remain infective for up to a week. With contact, the larvae penetrate skin and migrate in the bloodstream to the pulmonary capillaries. In the lungs, the larvae penetrate into alveoli and then are carried by ciliary action upward to the bronchi, trachea, and mouth. After being swallowed, they reach and attach to the mucosa of the upper small bowel, where they mature to adult worms. *Ancylostoma* infection can also be acquired by ingestion of the larvae in food or water. Hookworms attach to the intestinal mucosa and suck blood. Blood loss is proportionate to the worm burden.

► Clinical Findings

A. Symptoms and Signs

Most infected persons are asymptomatic. A pruritic maculopapular rash (ground itch) may occur at the site of larval penetration, usually in previously sensitized persons. Pulmonary symptoms may be seen during larval migration through the lungs, with dry cough, wheezing, and low-grade fever, but these symptoms are less common than with ascariasis. About 1 month after infection, as maturing worms attach to the small intestinal mucosa, gastrointestinal symptoms may develop, with epigastric pain, anorexia, and diarrhea, especially in previously unexposed individuals. Persons chronically infected with large worm burdens may have abdominal pain, anorexia, diarrhea, and findings of marked iron-deficiency anemia and protein malnutrition. Anemia can lead to pallor, weakness, dyspnea, and heart failure, and protein loss can lead to hypoalbuminemia, edema, and ascites. These findings may be accompanied by impairment in growth and cognitive development in children. Infection with the dog hookworm *Ancylostoma caninum* can uncommonly lead to abdominal pain, diarrhea, and eosinophilia, with intestinal ulcerations and regional lymphadenitis.

B. Laboratory Findings

Diagnosis is based on the demonstration of characteristic eggs in feces; concentration techniques are usually not needed. Microcytic anemia, occult blood in the stool, and hypoalbuminemia are common. Eosinophilia is common, especially during worm migration.

► Treatment

Treatment is with albendazole (single 400-mg oral dose) or mebendazole (100 mg orally twice daily for 3 days).

Occasional adverse effects are diarrhea and abdominal pain. Pyrantel pamoate and levamisole are also effective. Anemia should be managed with iron replacement and, for severe symptomatic anemia, blood transfusion. Mass treatment of children with single doses of albendazole or mebendazole at regular intervals limits worm burdens and the extent of disease and is advocated by WHO.

STRONGYLOIDIASIS



ESSENTIALS OF DIAGNOSIS

- ▶ Transient pruritic skin rash and lung symptoms.
- ▶ Anorexia, diarrhea, abdominal discomfort.
- ▶ Larvae detected in stool.
- ▶ Hyperinfection in the immunocompromised; larvae detected in sputum or other fluids.
- ▶ Eosinophilia.

General Considerations

Strongyloidiasis is caused by infection with *Strongyloides stercoralis*. Although much less prevalent than ascariasis, trichuriasis, or hookworm infections, strongyloidiasis is nonetheless a significant problem, infecting tens of millions of individuals in tropical and subtropical regions. Infection is also endemic in some temperate regions of North America, Europe, Japan, and Australia. Of particular importance is the predilection of the parasite to cause severe infections in immunocompromised individuals due to its ability to replicate in humans. A related parasite, *Strongyloides fuelleborni*, infects humans in parts of Africa and New Guinea.

Among nematodes, *S. stercoralis* is uniquely capable of maintaining its full life cycle both within the human host and in soil. Infection occurs when filariform larvae in soil penetrate the skin, enter the bloodstream, and are carried to the lungs, where they escape from capillaries into alveoli, ascend the bronchial tree, and are then swallowed and carried to the duodenum and upper jejunum, where maturation to the adult stage takes place. Females live embedded in the mucosa for up to 5 years, releasing eggs that hatch in the intestines as free rhabditiform larvae that pass to the ground via the feces. In moist soil, these larvae metamorphose into infective filariform larvae. Autoinfection can occur in humans, when some rhabditiform larvae develop into filariform larvae that penetrate the intestinal mucosa or perianal skin, and enter the circulation. The most dangerous manifestation of *S. stercoralis* infection is the **hyperinfection syndrome**, with dissemination of large numbers of filariform larvae to the lungs and other tissues in immunocompromised individuals. Mortality with this syndrome approaches 100% without treatment and has been about 25% with treatment. The hyperinfection syndrome is seen in patients receiving corticosteroids and other immunosuppressive medications; patients with hematologic malignancies, malnutrition, or alcoholism; or persons with

AIDS. The risk seems greatest for those receiving corticosteroids.

Clinical Findings

A. Symptoms and Signs

As with other intestinal nematodes, most infected persons are asymptomatic. An acute syndrome can be seen at the time of infection, with a pruritic, erythematous, maculopapular rash, usually of the feet. These symptoms may be followed by pulmonary symptoms (including dry cough, dyspnea, and wheezing) and eosinophilia after a number of days, followed by gastrointestinal symptoms after some weeks, as with hookworm infections. Chronic infection may be accompanied by epigastric pain, nausea, diarrhea, and anemia. Maculopapular or urticarial rashes of the buttocks, perineum, and thighs, due to migrating larvae, may be seen. Large worm burdens can lead to malabsorption or intestinal obstruction. Eosinophilia is common but may fluctuate.

With hyperinfection large numbers of larvae can migrate to many tissues, including the lungs, CNS, kidneys, and liver. Gastrointestinal symptoms can include abdominal pain, nausea, vomiting, diarrhea, and more severe findings related to intestinal obstruction, perforation, or hemorrhage. Bacterial sepsis, probably secondary to intestinal ulcerations, is a common presenting finding. Pulmonary findings include pneumonitis, cough, hemoptysis, and respiratory failure. Sputum may contain adult worms, larvae, and eggs. CNS disease includes meningitis and brain abscesses; the CSF may contain larvae. Various presentations can progress to shock and death.

B. Laboratory Findings

The diagnosis of strongyloidiasis can be difficult, as eggs are seldom found in feces. Diagnosis is usually based on the identification of rhabditiform larvae in the stool or duodenal contents. These larvae must be distinguished from hookworm larvae, which may hatch after stool collection. Repeated examinations of stool or examination of duodenal fluid may be required for diagnosis because the sensitivity of individual tests is only about 30%. Hyperinfection is diagnosed by the identification of large numbers of larvae in stool, sputum, or other body fluids. An ELISA from the CDC offers about 90% sensitivity and specificity, but cross-reactions with other helminths may occur. PCR and related molecular diagnostic methods have improved and are useful diagnostic tests. Eosinophilia and mild anemia are common, but eosinophilia may be absent with hyperinfection. Hyperinfection may include extensive pulmonary infiltrates, hypoproteinemia, and abnormal liver function studies.

C. Screening

It is important to be aware of the possibility of strongyloidiasis in persons with even a distant history of residence in an endemic area, since the infection can be latent for decades. Screening of at-risk individuals for infection is appropriate before institution of immunosuppressive

therapy. Screening can consist of serologic tests, with stool examinations in those with positive serologic tests, but consideration of presumptive treatment even if the stool evaluations are negative.

► Treatment

Full eradication of *S stercoralis* is more important than with other intestinal helminths due to the ability of the parasite to replicate in humans. The treatment of choice for routine infection is ivermectin (200 mcg/kg orally daily for 1–2 days). Less effective alternatives are albendazole (400 mg orally twice daily for 3 days) and thiabendazole (25 mg/kg orally twice daily for 3 days). For hyperinfection, ivermectin should be administered daily until the clinical syndrome has resolved and larvae have not been identified for at least 2 weeks. Follow-up examinations for larvae in stool or sputum are necessary, with repeat dosing if the infection persists. With continued immunosuppression, eradication may be difficult, and regular repeated therapy (eg, monthly ivermectin) may be required.

ENTEROBIASIS



ESSENTIALS OF DIAGNOSIS

- ▶ Nocturnal perianal pruritus.
- ▶ Identification of eggs or adult worms on perianal skin or in stool.

► General Considerations

Enterobius vermicularis, the pinworm, is a common cause of intestinal infections worldwide, with maximal prevalence in school-aged children. Enterobiasis is transmitted person-to-person via ingestion of eggs after contact with the hands or perianal region of an infected individual, food or fomites that have been contaminated by an infected individual, or infected bedding or clothing. Autoinfection also occurs. Eggs hatch in the duodenum and larvae migrate to the cecum. Females mature in about a month, and remain viable for about another month. During this time, they migrate through the anus to deposit large numbers of eggs on the perianal skin. Due to the relatively short life span of these helminths, continuous reinfection, as in institutional settings, is required for long-standing infection.

► Clinical Findings

A. Symptoms and Signs

Most individuals with pinworm infection are asymptomatic. The most common symptom is perianal pruritus, particularly at night, due to the presence of the female worms or deposited eggs. Insomnia, restlessness, and enuresis are common in children. Perianal scratching may result in excoriation and impetigo. Many mild gastrointestinal symptoms have also been attributed to enterobiasis, but associations are not proven. Serious sequelae are

uncommon. Rarely, worm migration results in inflammation or granulomatous reactions of the gastrointestinal or genitourinary tracts. Colonic ulceration and eosinophilic colitis have been reported.

B. Laboratory Findings

Pinworm eggs are usually not found in stool. Diagnosis is made by finding adult worms or eggs on the perianal skin. A common test is to apply clear cellophane tape to the perianal skin, ideally in the early morning, followed by microscopic examination for eggs. The sensitivity of the tape test is reported to be about 50% for a single test and 90% for three tests. Nocturnal examination of the perianal area or gross examination of stools may reveal adult worms, which are about 1 cm in length. Eosinophilia is rare.

► Treatment

Treatment is with single oral doses of albendazole (400 mg), mebendazole (100 mg), or pyrantel pamoate (11 mg/kg, to a maximum of 1 g). The dose is repeated in 2 weeks due to frequent reinfection. Other infected family members should be treated concurrently, and treatment of all close contacts may be appropriate when rates of reinfection are high in family, school, or institutional settings. Standard hand washing and hygiene practices are helpful in limiting spread. Perianal scratching should be discouraged. Washing of clothes and bedding should kill pinworm eggs.

Else KJ et al. Whipworm and roundworm infections. Nat Rev Dis Primers. 2020;6:44. [PMID: 32467581]

Jourdan PM et al. Soil-transmitted helminth infections. Lancet. 2018;391:252. [PMID: 28882382]

Krolewiecki A et al. Strongyloidiasis: a neglected tropical disease.

Infect Dis Clin North Am. 2019;33:135. [PMID: 30712758]

Moser W et al. Drug combinations against soil-transmitted helminth infections. Adv Parasitol. 2019;103:91. [PMID: 30878060]

INVASIVE NEMATODE (Roundworm) INFECTIONS

ANGIOSTRONGYLIASIS

Nematodes of rats of the genus *Angiostrongylus* cause two distinct syndromes in humans. *Angiostrongylus cantonensis*, the rat lungworm, causes eosinophilic meningoencephalitis, primarily in Southeast Asia and some Pacific islands, but with multiple recent reports also from the Americas, Hawaii (82 reported cases in 2007–17), and Australia. In one study, *A cantonensis* was responsible for 67% of evaluable cases of eosinophilic meningitis in Vietnam. *Angiostrongylus costaricensis* causes gastrointestinal inflammation. In both diseases, human infection follows ingestion of larvae within slugs or snails (and also crabs, prawns, or centipedes for *A cantonensis*) or on material, such as salads, contaminated by these organisms. Since the parasites are not in their natural hosts, they cannot complete their life cycles, but they can cause disease after migrating to the brain or gastrointestinal tract. *A cantonensis* can also migrate from the brain to the pulmonary arteries.

► Clinical Findings

A. *A cantonensis* Infection

The disease is caused primarily by worm larvae migrating through the CNS and an inflammatory response to dying worms. After an incubation period of 1 day to 2 weeks, presenting symptoms and signs include headache, stiff neck, nausea, vomiting, cranial nerve abnormalities, and paresthesias. Most cases resolve spontaneously after 2–8 weeks, but serious sequelae and death have been reported. The diagnosis is strongly suggested by the finding of eosinophilic CSF pleocytosis (over 10% eosinophils) in a patient with a history of travel to an endemic area. Peripheral eosinophilia may not be present. Definitive diagnosis is made by recovery of *A cantonensis* larvae from the CSF and the eyes, although this is uncommon.

B. *A costaricensis* Infection

Parasites penetrate ileocecal vasculature and develop into adults, which lay eggs, but do not complete their life cycle. Disease is due to an inflammatory response to dying worms in the intestinal tract, with an eosinophilic granulomatous response, at times including vasculitis and ischemic necrosis. Common findings are abdominal pain, vomiting, and fever. Pain is most commonly localized to the right lower quadrant, and a mass may be appreciated, all mimicking appendicitis. Symptoms may recur over months. Uncommon findings are intestinal perforation or obstruction, or disease due to migration of worms to other sites. Many cases are managed surgically, usually for suspected appendicitis. Biopsy of inflamed intestinal tissue may show worms localized to mesenteric arteries and eosinophilic granulomas.

► Treatment

Antihelminthic therapy may be harmful for *A cantonensis* infection, since responses to dying worms may worsen with therapy. If antihelminthic treatment is to be used, albendazole is probably the best choice, and therapy should be early in the disease course (within 3 weeks of exposure). Corticosteroids have commonly been used, and these are probably appropriate if antihelminthics are provided. Ocular infection is treated surgically. It is not known if antihelminthic therapy is helpful for *A costaricensis* infection.

Johnston DI et al. Review of cases of angiostrongyliasis in Hawaii, 2007–2017. *Am J Trop Med Hyg*. 2019;101:608. [PMID: 31287041]
 McAuliffe L et al. Severe CNS angiostrongyliasis in a young marine: a case report and literature review. *Lancet Infect Dis*. 2019;19:e132. [PMID: 30454904]

CUTANEOUS LARVA MIGRANS (Creeping Eruption)

Cutaneous larva migrans is caused principally by larvae of the dog and cat hookworms, *Ancylostoma braziliense* and *A caninum*. Other animal hookworms, gnathostomiasis, and strongyloidiasis may also cause this syndrome. Infections are common in warm areas, including the southeastern United States. They are most common in children. The disease is caused by the migration of worms through skin;



▲ **Figure 35–8.** Cutaneous larva migrans on the foot.

(Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

the nonhuman parasites cannot complete their life cycles, so only cause cutaneous disease.

► Clinical Findings

Intensely pruritic erythematous papules develop, usually on the feet or hands, followed within a few days by serpiginous tracks marking the course of the parasite, which may travel several millimeters per day (Figure 35–8). Several tracks may be present. The process may continue for weeks, with lesions becoming vesiculated, encrusted, or secondarily infected. Systemic symptoms and eosinophilia are uncommon.

The diagnosis is based on the characteristic appearance of the lesions. Biopsy is usually not indicated.

► Treatment

Without treatment, the larvae eventually die and are absorbed. Mild cases do not require treatment. Thiabendazole (10% aqueous suspension) can be applied topically three times daily for 5 or more days. Systemic therapy with albendazole (400 mg orally once or twice daily for 3–5 days) or ivermectin (200 mcg/kg orally single dose) is highly effective.

Kincaid L et al. Management of imported cutaneous larva migrans: a case series and mini-review. *Travel Med Infect Dis*. 2015;13:382. [PMID: 2624336]

FILARIASIS

LYMPHATIC FILARIASIS

► ESSENTIALS OF DIAGNOSIS

- Episodic attacks of lymphangitis, lymphadenitis, and fever.
- Chronic progressive swelling of extremities and genitalia; hydrocele; chyluria; lymphedema.
- Microfilariae in blood, chyluria, or hydrocele fluid; positive serologic tests.

► General Considerations

Lymphatic filariasis is caused by three filarial nematodes: *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*, and is among the most important parasitic diseases of man. Approximately 120 million people are infected with these organisms in tropical and subtropical countries, about a third of these suffer clinical consequences of the infections, and many are seriously disfigured. *W bancrofti* causes about 90% of episodes of lymphatic filariasis. It is transmitted by *Culex*, *Aedes*, and *Anopheles* mosquitoes and is widely distributed in the tropics and subtropics, including sub-Saharan Africa, Southeast Asia, the western Pacific, India, South America, and the Caribbean. *B malayi* is transmitted by *Mansonia* and *Anopheles* mosquitoes and is endemic in parts of China, India, Southeast Asia, and the Pacific. *B timori* is found only in islands of southeastern Indonesia. *Mansonella* are filarial worms transmitted by midges and other insects in Africa and South America.

Humans are infected by the bites of infected mosquitoes. Larvae then move to the lymphatics and lymph nodes, where they mature over months to thread-like adult worms, and then can persist for many years. The adult worms produce large numbers of microfilariae, which are released into the circulation, and infective to mosquitoes, particularly at night (except for the South Pacific, where microfilaremia peaks during daylight hours).

► Clinical Findings

A. Symptoms and Signs

Many infections remain asymptomatic despite circulating microfilariae. Clinical consequences of filarial infection are principally due to inflammatory responses to developing, mature, and dying worms. The initial manifestation of infection is often acute lymphangitis, with fever, painful lymph nodes, edema, and inflammation spreading peripherally from involved lymph nodes (in contrast to bacterial lymphangitis, which spreads centrally). Lymphangitis and lymphadenitis of the upper and lower extremities is common (Figure 35–9); genital involvement, including epididymitis and orchitis, with scrotal pain and tenderness, occurs principally only with *W bancrofti* infection. Acute attacks of lymphangitis last for a few days to a week and may recur a few times per year. Filarial fevers may also occur without lymphatic inflammation.

The most common chronic manifestation of lymphatic filariasis is swelling of the extremities or genitals due to chronic lymphatic inflammation and obstruction. Extremities become increasingly swollen, with a progression over time from pitting edema, to nonpitting edema, to sclerotic changes of the skin that are referred to as elephantiasis. Genital involvement, particularly with *W bancrofti*, occurs more commonly in men, progressing from painful epididymitis to hydroceles that are usually painless but can become very large, with inguinal lymphadenopathy, thickening of the spermatic cord, scrotal lymphedema, thickening and fissuring of the scrotal skin, and occasionally chyluria. Lymphedema of the female genitalia and breasts may also occur.



▲ **Figure 35–9.** Elephantiasis of legs due to filariasis.
(Public Health Image Library, CDC.)

Tropical pulmonary eosinophilia is a distinct syndrome principally affecting young adult males with either *W bancrofti* or *B malayi* infection, but typically without microfilaremia. This syndrome is characterized by asthma-like symptoms, with cough, wheezing, dyspnea, and low-grade fevers, usually at night. Without treatment, tropical pulmonary eosinophilia can progress to interstitial fibrosis and chronic restrictive lung disease. *Mansonella* can inhabit serous cavities, the retroperitoneum, the eye, or the skin, and cause abnormalities related to inflammation at these sites.

B. Laboratory Findings

The diagnosis of lymphatic filariasis is strongly suggested by characteristic findings of lymphangitis or lymphatic obstruction in persons with risk factors for the disease. The diagnosis is confirmed by finding microfilariae, usually in blood, but microfilariae may be absent, especially early in the disease progression (first 2–3 years) or with chronic obstructive disease. To increase yields, blood samples are obtained at about midnight in most areas, but during daylight hours in the South Pacific. Smears are evaluated by wet mount to identify motile parasites and by Giemsa staining; these examinations can be delayed until the following morning, with storage of samples at room temperature. Of note, the periodicity of microfilaremia is variable, and daytime samples may yield positive results. Microfilariae may also be identified in hydrocele fluid or chylous urine. Eosinophilia is usually absent, except during acute inflammatory syndromes. Serologic tests may be helpful but cannot distinguish past and active infections. Rapid antigen tests with sensitivity and specificity over 90% are available for detection of *W bancrofti*. These can be considered the diagnostic tests of choice and are used to guide control programs. However, cross-reactivity with *Loa loa* infections has been described. Due to potential severe toxicity, caution is appropriate before treatment with

ivermectin for positive *W bancrofti* antigen tests in areas also endemic for *L loa* infection. Multiple molecular tests, including field-friendly LAMP assays, have been developed. Adult worms may also be found in lymph node biopsy specimens (although biopsy is not usually clinically indicated) or by ultrasound of a scrotal hydrocele or lymphedematous breast. When microfilaremia is lacking, especially if sophisticated techniques are not available, diagnoses may need to be made on clinical grounds.

► Treatment & Control

A. Drug Treatment

Diethylcarbamazine is the drug of choice, but it cannot cure infections due to its limited action against adult worms. Asymptomatic infection and acute lymphangitis are treated with this drug (2 mg/kg orally three times daily) for 10–14 days, leading to a marked decrease in microfilaremia. Therapy may be accompanied by allergic symptoms, including fever, headache, malaise, hypotension, and bronchospasm, probably due to release of antigens from dying worms. For this reason, treatment courses may begin with a lower dosage, with escalation over the first 4 days of treatment. Single annual doses of diethylcarbamazine (6 mg/kg orally), alone or with ivermectin (400 mcg/kg orally) or albendazole (400 mg orally) may be as effective as longer courses of diethylcarbamazine. Combination therapy with a single dose of each of the three drugs cleared parasites in more than 95% of persons for 3 years and offered superior clearance compared to a single dose of diethylcarbamazine plus albendazole and noninferiority compared to three annual doses of the two-drug regimen; triple-drug therapy was as safe and well-tolerated. When onchocerciasis or loiasis is suspected, it may be appropriate to withhold diethylcarbamazine to avoid severe reactions to dying microfilariae; rather, ivermectin plus albendazole may be given, although these drugs are less active than diethylcarbamazine against adult worms. Appropriate management of advanced obstructive disease is uncertain. Drainage of hydroceles provides symptomatic relief, although they will recur. Therapy with diethylcarbamazine cannot reverse chronic lymphatic changes, but is typically provided to lower worm burdens. An interesting approach under study is to treat with doxycycline (100–200 mg/day orally for 4–6 weeks), which kills obligate intracellular *Wolbachia* bacteria, leading to death of adult filarial worms. Doxycycline was also effective at controlling *Mansonella perstans* infection, which does not respond well to standard antifilarial drugs. Secondary bacterial infections must be treated. Surgical correction may be helpful in some cases.

B. Disease Control

Avoidance of mosquitoes is a key measure; preventive measures include the use of screens, bed nets (ideally treated with insecticide), and insect repellents. Community-based treatment with single annual doses of effective drugs offers a highly effective means of control. The current WHO strategy for control includes mass treatment of at-risk communities with single annual doses of diethylcarbamazine

plus albendazole or, for areas with onchocerciasis, albendazole plus ivermectin; in some circumstances, more frequent dosing offers improved control.

Dubray CL et al. Safety and efficacy of co-administered diethylcarbamazine, albendazole and ivermectin during mass drug administration for lymphatic filariasis in Haiti: results from a two-armed, open-label, cluster-randomized, community study. *PLoS Negl Trop Dis.* 2020;14:e0008298. [PMID: 32511226]

King CL et al. A trial of a triple-drug treatment for lymphatic filariasis. *N Engl J Med.* 2018;379:1801. [PMID: 30403937]

Weil GJ et al. The safety of double- and triple-drug community mass drug administration for lymphatic filariasis: a multicenter, open-label, cluster-randomized study. *PLoS Med.* 2019;16:e1002839. [PMID: 31233507]

ONCHOCERCIASIS



ESSENTIALS OF DIAGNOSIS

- Conjunctivitis progressing to blindness.
- Severe pruritus; skin excoriations, thickening, and depigmentation; and subcutaneous nodules.
- Microfilariae in skin snips and on slit-lamp examination; adult worms in subcutaneous nodules.

► General Considerations

Onchocerciasis, or river blindness, is caused by *Onchocerca volvulus*. An estimated 37 million persons are infected, of whom 3–4 million have skin disease, 500,000 have severe visual impairment, and 300,000 are blinded. Over 99% of infections are in sub-Saharan Africa, especially the West African savanna, with about half of cases in Nigeria and Congo. In some hyperendemic African villages, close to 100% of individuals are infected, and 10% or more of the population is blind. The disease is also prevalent in the southwestern Arabian Peninsula and Latin America, including southern Mexico, Guatemala, Venezuela, Colombia, Ecuador, and northwestern Brazil. Onchocerciasis is transmitted by simuliid flies (blackflies). These insects breed in fast-flowing streams and bite during the day.

After the bite of an infected blackfly, larvae are deposited in the skin, where adults develop over 6–12 months. Adult worms live in subcutaneous connective tissue or muscle nodules for a decade or more. Microfilariae are released from the nodules and migrate through subcutaneous and ocular tissues. Disease is due to responses to worms and to intracellular *Wolbachia* bacteria.

► Clinical Findings

A. Symptoms and Signs

After an incubation period of up to 1–3 years, the disease typically produces an erythematous, papular, pruritic rash, which may progress to chronic skin thickening and

depigmentation. Itching may be severe and unresponsive to medications, such that more disability-adjusted life-years are lost to onchocercal skin problems than to blindness. Numerous firm, nontender, movable subcutaneous nodules of about 0.5–3 cm, which contain adult worms, may be present. Due to differences in vector habits, these nodules are more commonly on the lower body in Africa but on the head and upper body in Latin America. Inguinal and femoral lymphadenopathy is common, at times resulting in a “hanging groin,” with lymph nodes hanging within a sling of atrophic skin. Patients may also have systemic symptoms, with weight loss and musculoskeletal pain.

The most serious manifestations of onchocerciasis involve the eyes. Microfilariae migrating through the eyes elicit host responses that lead to pathology. Findings include punctate keratitis and corneal opacities, progressing to sclerosing keratitis and blindness. Iridocyclitis, glaucoma, choroiditis, and optic atrophy may also lead to vision loss. The likelihood of blindness after infection varies greatly based on geography, with the risk greatest in savanna regions of West Africa.

B. Diagnostic Testing

The diagnosis is made by identifying microfilariae in skin snips, by visualizing microfilariae in the cornea or anterior chamber by slit-lamp examination, by identification of adult worms in a biopsy or aspirate of a nodule or, uncommonly, by identification of microfilariae in urine. Skin snips from the iliac crest (Africa) or scapula (Americas) are allowed to stand in saline for 2–4 hours or longer, and then examined microscopically for microfilariae. Deep punch biopsies are not needed, and if suspicion persists after a skin snip is negative, the procedure should be repeated. Ultrasound may identify characteristic findings suggestive of adult worms in skin nodules. When the diagnosis remains difficult, the Mazzotti test can be used; exacerbation of skin rash and pruritus after a 50-mg oral dose of diethylcarbamazine is highly suggestive of the diagnosis. This test should only be used after other tests are negative, since treatment can elicit severe skin and eye reactions in heavily infected individuals. A related and safer test using topical diethylcarbamazine is also available. Eosinophilia is a common but inconsistent finding. Antigen and antibody detection tests are under study.

Treatment & Control

The treatment of choice is ivermectin, which kills microfilariae, but not adult worms, so disease control requires repeat administrations. Treatment is with a single oral dose of 150 mcg/mL, but schedules for re-treatment have not been standardized. One regimen is to treat every 3 months for 1 year, followed by treatment every 6–12 months for the suspected life span of adult worms (about 15 years). Treatment results in marked reduction in numbers of microfilariae in the skin and eyes, although its impact on the progression of visual loss remains uncertain. Toxicities of ivermectin are generally mild; fever, pruritus, urticaria, myalgias, edema, hypotension, and tender lymphadenopathy may be seen, presumably due to reactions to dying worms. Ivermectin should be used with caution in patients also at risk for loiasis, since it can elicit severe reactions including encephalopathy. Moxidectin, which is used for many veterinary parasitic infections, was approved by the FDA for the treatment of onchocerciasis in 2018. Moxidectin was well-tolerated and superior to ivermectin in suppressing skin microfilariae and offers another agent for treatment and control. As with other filarial infections, doxycycline acts against *O volvulus* by killing intracellular *Wolbachia* bacteria. A course of 100 mg/day for 4–6 weeks kills the bacteria and prevents parasite embryogenesis for at least 18 months. Doxycycline shows promise as a first-line agent to treat onchocerciasis because of its improved activity against adult worms compared to other agents and limited toxicity due to the slow action of the drug.

Protection against onchocerciasis includes avoidance of biting flies. Major efforts are underway to control insect vectors in Africa. In addition, mass distribution of ivermectin for intermittent administration at the community level is ongoing, and the prevalence of severe skin and eye disease is decreasing.

Opoku NO et al. Single dose moxidectin versus ivermectin for *Onchocerca volvulus* infection in Ghana, Liberia, and the Democratic Republic of the Congo: a randomised, controlled, double-blind phase 3 trial. Lancet. 2018;392:1207. [PMID: 29361335]

Mycotic Infections

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CANDIDIASIS



ESSENTIALS OF DIAGNOSIS

- ▶ Common normal flora but opportunistic pathogen.
- ▶ Typically mucosal disease, particularly vaginitis and oral thrush/esophagitis.
- ▶ Persistent, unexplained oral or vaginal candidiasis: check for HIV or diabetes mellitus.
- ▶ (1,3)-Beta-D-glucan results may be positive in candidemia even when blood cultures are negative.

► General Considerations

Candida albicans can be cultured from the mouth, vagina, and feces of most people. Cellular immunodeficiency predisposes to mucocutaneous disease. When no other underlying cause is found, persistent oral or vaginal candidiasis should raise suspicion for HIV infection or diabetes. Risk factors for invasive candidiasis include prolonged neutropenia, abdominal surgery, broad-spectrum antibiotic therapy, corticosteroids, kidney disease, and the presence of intravascular catheters. Although *C albicans* remains the most common cause of both mucocutaneous and systemic candidiasis, non-*albicans* strains are of considerable importance in certain contexts and may impact therapy owing to antifungal resistance.

► Clinical Findings

A. Mucosal Candidiasis

Vulvovaginal candidiasis occurs in an estimated 75% of women during their lifetime. Risk factors include pregnancy, uncontrolled diabetes mellitus, broad-spectrum antimicrobial treatment, corticosteroid use, and HIV infection. Symptoms include acute vulvar pruritus, burning vaginal discharge, and dyspareunia.

Esophageal candidiasis may present clinically with symptoms of substernal odynophagia, gastroesophageal reflux, or nausea without substernal pain. Oral candidiasis,

though often associated, is not invariably present. Diagnosis is best confirmed by endoscopy with biopsy and culture.

B. Candidal Funguria

Most cases of candidal funguria are asymptomatic and represent specimen contamination or bladder colonization (and do not warrant antifungal therapy). However, symptoms and signs of true *Candida* urinary tract infections are indistinguishable from bacterial urinary tract infections and can include urgency, hesitancy, fever, chills, or flank pain.

C. Invasive Candidiasis

Invasive candidiasis can be (1) candidemia (bloodstream infection) without deep-seated infection; (2) candidemia with deep-seated infection (typically eyes, kidney, or abdomen); and (3) deep-seated candidiasis in the absence of bloodstream infection (ie, hepatosplenic candidiasis). Varying ratios of these clinical entities depends on the predominating risk factors for affected patients (ie, neutropenia, indwelling vascular catheters, postsurgical).

The clinical presentation of candidemia varies from minimal fever to septic shock that can resemble a severe bacterial infection. The diagnosis of invasive *Candida* infection is challenging, since *Candida* species are often isolated from mucosal sites in the absence of invasive disease while blood cultures are positive only 50% of the time in invasive infection. Consecutively positive (1,3)-beta-D-glucan results may be used to guide empiric therapy in high-risk patients even in the absence of positive blood cultures.

Hepatosplenic candidiasis can occur following prolonged neutropenia in patients with underlying hematologic cancers, but this entity is less common in the era of widespread antifungal prophylaxis. Typically, fever and variable abdominal pain present weeks after chemotherapy when neutrophil counts have recovered. Blood cultures are generally negative, though hepatosplenic abscesses may be seen on abdominal imaging.

D. Candidal Endocarditis

Candidal endocarditis is a rare infection affecting patients with prosthetic heart valves or prolonged candidemia, such

as with indwelling catheters. The diagnosis is established definitively by culturing *Candida* from vegetations at the time of valve replacement.

Treatment

A. Mucosal Candidiasis

Vulvovaginal candidiasis can be treated with topical or oral azoles. A single 150-mg oral dose of fluconazole is equivalent to topical treatments with better patient acceptance. Topical azole preparations include clotrimazole, 100-mg vaginal tablet for 7 days, or miconazole, 200-mg vaginal suppository for 3 days. Disease recurrence is common but can be decreased with weekly oral fluconazole therapy (150 mg weekly). Vulvovaginal candidiasis caused by non-*albicans* strains (eg, *Candida glabrata*) may require alternative therapies (such as intravaginal boric acid) in the setting of azole resistance. Oral ibrexafungerp, a highly bioavailable glucan synthase inhibitor, may also be effective for azole-resistant disease.

Treatment of **esophageal candidiasis** depends on the severity of disease. If patients are able to swallow and take adequate amounts of fluid orally, fluconazole, 200–400 mg daily for 14–21 days, is recommended. Patients who are unable to tolerate oral therapy should receive intravenous fluconazole, 400 mg daily, or an echinocandin. Options for patients with fluconazole-refractory disease include oral itraconazole solution, 200 mg daily; oral or intravenous voriconazole, 200 mg twice daily; or an intravenous echinocandin (caspofungin, 70 mg loading dose, then 50 mg/day; anidulafungin, 200 mg/day; or intravenous micafungin, 150 mg/day). Posaconazole tablets, 300 mg/day, may also be considered for fluconazole-refractory disease. Relapse is common with all agents when there is underlying HIV infection without adequate immune reconstitution.

B. Candidal Funguria

Candidal funguria frequently resolves with discontinuance of antibiotics or removal of bladder catheters. Clinical benefit from treatment of asymptomatic candiduria has not been demonstrated, but persistent funguria should raise the suspicion of invasive infection. When symptomatic funguria persists, oral fluconazole, 200 mg/day for 7–14 days, can be used.

C. Invasive Candidiasis

The 2016 Infectious Diseases Society of America guidelines for management of candidemia recommend an intravenous echinocandin as first-line therapy (ie, caspofungin (70 mg once, then 50 mg daily), micafungin (100 mg daily), or anidulafungin (200 mg once, then 100 mg daily)). Intravenous or oral fluconazole (800 mg once, then 400 mg daily) is an acceptable alternative for less critically ill patients without recent azole exposure.

Therapy for candidemia should be continued for 2 weeks after the last positive blood culture and resolution of symptoms and signs of infection. A dilated fundoscopic

examination is recommended for patients with candidemia to exclude endophthalmitis and repeat blood cultures should be drawn to demonstrate organism clearance. Susceptibility testing is recommended on all bloodstream *Candida* isolates; once patients have become clinically stable, parenteral therapy can be discontinued and treatment can be completed with oral fluconazole, 400 mg daily for susceptible isolates. Removal or exchange of intravascular catheters is recommended for patients with candidemia in whom the catheter is the suspected source of infection.

Non-*albicans* species of *Candida* often have resistance patterns that are different from *C albicans*. An echinocandin is recommended for treatment of *C glabrata* infection with transition to oral fluconazole or voriconazole reserved for patients whose isolates are known to be susceptible to these agents. For isolates with resistance to azoles and echinocandins, lipid formulation amphotericin B (3–5 mg/kg intravenously daily) may be used. *C krusei* is generally fluconazole-resistant and so should be treated with an alternative agent, such as an echinocandin or voriconazole. Cases of health care-associated infections due to multi-drug-resistant *Candida auris* have been described from several countries, including the United States, with most cases having been treated with echinocandins plus environmental source control.

D. Candidal Endocarditis

Best results are achieved with a combination of medical and surgical therapy (valve replacement). Lipid formulation amphotericin B (3–5 mg/kg/day) or high-dose echinocandin (caspofungin 150 mg/day, micafungin 150 mg/day, or anidulafungin 200 mg/day) is recommended as initial therapy. Step-down or long-term suppressive therapy for nonsurgical candidates may be done with fluconazole at 6–12 mg/kg/day for susceptible organisms.

E. Prevention of Invasive Candidiasis

In high-risk patients undergoing induction chemotherapy, bone marrow transplantation, or liver transplantation, prophylaxis with antifungal agents has been shown to prevent invasive fungal infections, although the effect on mortality and the preferred agent remain debated. Although the isolation of *Candida* species from mucosal sites raises the possibility of invasive candidiasis among critically ill patients, trials of empiric antifungal agents in such situations have not shown clear clinical benefit.

Bradley SF. JAMA patient page. *Candida auris* infection. JAMA. 2019;322:1526. [PMID: 31613347]

Pappas PG et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:e1. [PMID: 26679628]

Pristov KE et al. Resistance of *Candida* to azoles and echinocandins worldwide. Clin Microbiol Infect. 2019;25:792. [PMID: 30965100]

HISTOPLASMOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Exposure to bird and bat droppings; common along river valleys (especially the Ohio River and the Mississippi River valleys).
- ▶ Most patients asymptomatic; respiratory illness most frequent clinical problem.
- ▶ Disseminated disease common in AIDS or other immunosuppressed states; poor prognosis.
- ▶ Blood and bone marrow cultures and urine polysaccharide antigen are useful in diagnosis of disseminated disease.

► General Considerations

Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic fungus that has been isolated from soil contaminated with bird or bat droppings in endemic areas (central and eastern United States, eastern Canada, Mexico, Central America, South America, Africa, and Southeast Asia). Infection presumably takes place by inhalation of conidia. These convert into small budding cells that are engulfed by phagocytes in the lungs. The organism proliferates and undergoes lymphohematogenous spread to other organs.

► Clinical Findings

A. Symptoms and Signs

Most cases of histoplasmosis are asymptomatic or mild and thus go unrecognized. Past infection is recognized by pulmonary and splenic calcification noted on incidental radiographs. Symptomatic infection may present with mild influenza-like illness, often lasting 1–4 days. Moderately severe infections are frequently diagnosed as atypical pneumonia. These patients have fever, cough, and mild central chest pain lasting 5–15 days.

Clinically evident infections occur in several forms: (1) **Acute pulmonary histoplasmosis** frequently occurs in epidemics, often when soil containing infected bird or bat droppings is disturbed. Clinical manifestations can vary from a mild influenza-like illness to severe pneumonia. The illness may last from 1 week to 6 months but is almost never fatal. (2) **Progressive disseminated histoplasmosis** most frequently occurs in patients with underlying HIV infection (with CD4 cell counts usually less than 100 cells/ μ L) or other conditions of impaired cellular immunity. Disseminated histoplasmosis has also been reported in patients from endemic areas taking tumor necrosis factor (TNF)-alpha inhibitors. It is characterized by fever and multiple organ system involvement. Chest radiographs may show a miliary pattern. Presentation may be fulminant, simulating septic shock, with death ensuing rapidly unless treatment is provided. Symptoms usually consist of

fever, dyspnea, cough, loss of weight, and prostration. Ulcers of the mucous membranes of the oropharynx may be present. The liver and spleen are nearly always enlarged, and all the organs of the body are involved, particularly the adrenal glands; *this results in adrenal insufficiency in about 50% of patients*. Gastrointestinal involvement may mimic inflammatory bowel disease. Central nervous system (CNS) invasion occurs in 5–10% of individuals with disseminated disease. (3) **Chronic pulmonary histoplasmosis** is usually seen in older patients who have underlying chronic lung disease. Chest radiographs show various lesions including complex apical cavities, infiltrates, and nodules. (4) **Complications of pulmonary histoplasmosis** include granulomatous mediastinitis characterized by persistently enlarged mediastinal lymph nodes and fibrosing mediastinitis in which an excessive fibrotic response to *Histoplasma* infection results in compromise of pulmonary vascular structures.

B. Laboratory Findings

Most patients with chronic pulmonary disease show anemia of chronic disease. Bone marrow involvement with pancytopenia may be prominent in disseminated forms. Marked lactate dehydrogenase (LD) and ferritin elevations are also common, as are mild elevations of serum aspartate aminotransferase.

With pulmonary involvement, sputum culture is rarely positive except in chronic disease; antigen testing of bronchoalveolar lavage fluid may be helpful in acute disease. The combination of urine and serum polysaccharide antigen assays has an 83% sensitivity for the diagnosis of acute pulmonary histoplasmosis.

Blood or bone marrow cultures from immunocompromised patients with acute disseminated disease are positive more than 80% of the time but may take several weeks for growth. The urine antigen assay has a sensitivity of greater than 90% for disseminated disease in immunocompromised patients and a declining titer can be used to follow response to therapy. Both CSF antigen and antibody testing should be performed in patients suspected of having meningitis.

► Treatment

For progressive localized disease and for mild to moderately severe nonmeningeal disseminated disease in immunocompetent or immunocompromised patients, itraconazole, 200–400 mg/day orally divided into two doses, is the treatment of choice with an overall response rate of approximately 80% (Table 36–1). The oral solution is better absorbed than the capsule formulation, which requires gastric acid for absorption. Therapeutic drug monitoring of itraconazole levels should be performed to assess adequacy of drug absorption. Duration of therapy ranges from weeks to several months depending on the severity of illness. Intravenous liposomal amphotericin B, 3 mg/kg/day, is used in patients with more severe disseminated disease and meningitis. Patients with AIDS-related histoplasmosis require lifelong suppressive therapy with itraconazole,

Table 36–1. Agents for systemic mycoses.*

Drug	Dosing	Renal Clearance?	CSF Penetration?	Toxicities	Spectrum of Activity
Polyenes					
Amphotericin B	0.3–1.5 mg/kg/day intravenously	No	Poor	Rigors, fever, azotemia, hypokalemia, hypomagnesemia, renal tubular acidosis, anemia	All major pathogens except <i>Scedosporium</i>
Amphotericin B lipid complex	5 mg/kg/day intravenously	No	Poor	Fever, rigors, nausea, hypotension, anemia, azotemia, tachypnea	Same as amphotericin B, above
Amphotericin B, liposomal	3–6 mg/kg/day intravenously	No	Poor	Fever, rigors, nausea, hypotension, azotemia, anemia, tachypnea, chest tightness	Same as amphotericin B, above Preferred agent for CNS
Azoles					
Fluconazole	Systemic infection: 400–2000 mg/day intravenously or orally Mucosal infection: 100–200 mg/day orally	Yes	Yes	Nausea, rash, xerosis, alopecia, headache, hepatic enzyme elevations	Mucosal candidiasis (including urinary tract), cryptococcosis, histoplasmosis, coccidioidomycosis
Isvuconazole	200 mg orally or intravenously every 8 hours for 6 doses (48 hours) as loading dose, followed by 200 mg/day orally or intravenously	No	Low in CSF, high in brain	Nausea, diarrhea, upper abdominal pain, dizziness	Broad range of activity including invasive aspergillosis and mucormycosis (limited data for <i>Mucorales</i>)
Itraconazole	Oral solution and capsule formulations available, both dosed at 200 mg three times daily for 3 days, then 200 mg once or twice daily thereafter ¹	No	Variable	Nausea, hypokalemia, edema, hypertension, peripheral neuropathy, exacerbation of heart failure	Histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, mucosal candidiasis (except urinary), sporotrichosis, aspergillosis, chromomycosis
SUBA-itraconazole	130 mg by mouth once daily (two 65-mg capsules)	No	Variable	Nausea, hypokalemia, edema, hypertension, peripheral neuropathy, exacerbation of heart failure	FDA-approved for treatment histoplasmosis, blastomycosis, aspergillosis
Ketoconazole	200–800 mg/day orally in one or two doses with food or acidic beverage	No	Poor	Anorexia, nausea, suppression of testosterone and cortisol, rash, headache, hepatic enzyme elevations, hepatic failure	Nonmeningeal histoplasmosis and coccidioidomycosis, blastomycosis, paracoccidioidomycosis, mucosal candidiasis (except urinary)
Posaconazole	Delayed-release tablet formulation preferred over oral solution due to more predictable absorption For delayed-release tablet or intravenous formulation: 300 mg twice daily for 2 doses (1 day) as loading dose followed by 300 mg daily thereafter	No	Yes	Nausea, vomiting, abdominal pain, diarrhea, and headache; pseudohyperaldosteronism	Broad range of activity including the <i>Mucorales</i>

(continued)

Table 36–1. Agents for systemic mycoses.* (continued)

Drug	Dosing	Renal Clearance?	CSF Penetration?	Toxicities	Spectrum of Activity
Azoles (cont.)					
Voriconazole ²	Systemic infection: 6 mg/kg intravenously every 12 hours for 24 hours loading dose, followed by 4 mg/kg intravenously every 12 hours or 200–300 mg orally every 12 hours Mucosal infection: 200–300 mg orally every 12 hours (no loading dose required)	Yes	Yes	Transient visual disturbances, rash, photosensitivity, fluoride excess with periostitis, peripheral neuropathy, squamous cell skin cancers, hepatic enzyme elevations ¹	All major pathogens except the <i>Mucorales</i> and sporotrichosis
Echinocandins					
Anidulafungin	200-mg intravenous loading dose, followed by 100 mg/day intravenously	< 1%	Poor	Diarrhea, hepatic enzyme elevations, histamine-mediated reactions	Mucosal and invasive candidiasis
Caspofungin acetate	70-mg intravenous loading dose, followed by 50 mg/day intravenously	< 50% ³	Poor	Transient neutropenia; hepatic enzyme elevations when used with cyclosporine	Aspergillosis, mucosal and invasive candidiasis, empiric antifungal therapy in febrile neutropenia
Micafungin sodium	100 mg/day intravenously	No	Poor	Rash, rigors, headache, phlebitis	Mucosal and invasive candidiasis, prophylaxis in hematopoietic stem cell transplantation
Antimetabolite					
Flucytosine (5-FC)	100–150 mg/kg/day orally in four divided doses	Yes	Yes	Leukopenia, ⁴ rash, diarrhea, hepatitis, nausea, vomiting	Cryptococcosis, ⁵ candidiasis, ⁵ chromomycosis
Allylamine					
Terbinafine	250 mg once daily orally	Yes	Poor	Nausea, abdominal pain, taste disturbance, rash, diarrhea, and hepatic enzyme elevations	Dermatophytes, sporotrichosis, chromomycosis, eumycetoma

*General information provided, but specific dosing may vary by indication and other patient characteristics; an infectious diseases specialist should be consulted for complex cases.

¹Oral solution preferred due to less variable absorption; capsule should be taken with food and acidic beverages to enhance absorption. For severe infections, blood levels should be measured to ensure adequate exposure.

²Some authorities advocate therapeutic drug monitoring in patients who are not responding to therapy. Administration with drugs that are metabolized by the cytochrome P450 system is contraindicated or requires careful monitoring of liver function. Intravenous formulation is contraindicated for patients with CrCl < 50 mL/min because of accumulation of cyclodextrin.

³No dosage adjustment required for chronic kidney disease; dosage adjustment necessary with moderate to severe hepatic dysfunction.

⁴Use should be monitored with blood levels to prevent this or the dose adjusted according to creatinine clearance.

⁵In combination with amphotericin B.

CNS, central nervous system; CSF, cerebrospinal fluid.

200 mg/day orally, although secondary prophylaxis may be discontinued if immune reconstitution occurs in response to antiretroviral therapy. Criteria for discontinuing secondary prophylaxis include 1 year of successful antifungal therapy along with a CD4 cell count of greater than 150 cells/mcL and 6 months or more of antiretroviral treatment (ART). There is no clear evidence that antifungal agents are of benefit for patients

with fibrosing mediastinitis, although oral itraconazole is often used. Rituximab, in conjunction with corticosteroids, may contribute to slowing progression of the fibrosing process and provide some clinical benefit. Reported outcomes in patients with fibrosing mediastinitis treated with either surgical procedures or nonsurgical intravascular interventions appear to be relatively good in the short term.

Azar MM et al. Current concepts in the epidemiology, diagnosis, and management of histoplasmosis syndromes. *Semin Respir Crit Care Med.* 2020;41:13. [PMID: 32000281]

COCCIDIODOMYCOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Acute infection: influenza-like illness, fever, backache, headache, fatigue, and cough. Erythema nodosum common.
- ▶ Dissemination may result in meningitis, bony lesions, or skin and soft tissue abscesses; common opportunistic infection in AIDS.
- ▶ Chest radiograph findings vary from pneumonitis to cavitation.
- ▶ Serologic tests useful; large spherules containing endospores demonstrable in sputum or tissues.

► General Considerations

Coccidioidomycosis should be considered in the diagnosis of any obscure illness in a patient who has lived in or visited an endemic area. Infection results from the inhalation of arthroconidia of *Coccidioides immitis* or *C posadasii*; both organisms are molds that grow in soil in certain arid regions of the southwestern United States, in Mexico, and in Central and South America. Less than 1% of immunocompetent persons show dissemination, but among these patients, the mortality rate is high.

In patients with AIDS who reside in endemic areas, coccidioidomycosis is a common opportunistic infection. In these patients, disease manifestations range from focal pulmonary infiltrates to widespread miliary disease with multiple organ involvement and meningitis; severity is inversely related to the extent of control of the HIV infection.

► Clinical Findings

A. Symptoms and Signs

Symptoms of **primary coccidioidomycosis** occur in about 40% of infections. Symptom onset (after an incubation period of 10–30 days) is usually that of a respiratory tract illness with fever and occasionally chills. Coccidioidomycosis is a common, frequently unrecognized, etiology of community-acquired pneumonia in endemic areas.

Erythema nodosum may appear 2–20 days after onset of symptoms. Persistent pulmonary lesions, varying from cavities and abscesses to parenchymal nodular densities or bronchiectasis, occur in about 5% of diagnosed cases.

Disseminated disease occurs in about 0.1% of White and 1% of non-White patients. Filipinos and Blacks are especially susceptible, as are pregnant women of all races. Any organ may be involved. Pulmonary findings usually become more pronounced, with mediastinal lymph node enlargement, cough, and increased sputum production. Lung abscesses may rupture into the pleural

space, producing an empyema. Complicated skin and bone infections may develop. Fungemia may occur and is characterized clinically by a diffuse miliary pattern on chest radiograph and by early death. The course may be particularly rapid in immunosuppressed patients. Clinicians caring for immunosuppressed patients in endemic areas need to consider that patients may be latently infected.

Meningitis occurs in 30–50% of cases of dissemination and may result in chronic basilar meningitis. Subcutaneous abscesses and verrucous skin lesions are especially common in fulminating cases. Patients with AIDS with disseminated disease have a higher incidence of miliary infiltrates, lymphadenopathy, and meningitis, but skin lesions are uncommon.

B. Laboratory Findings

In **primary coccidioidomycosis**, there may be moderate leukocytosis and eosinophilia. Serologic testing is useful for both diagnosis and prognosis. The immunodiffusion tube precipitin test and enzyme-linked immunosorbent assay (ELISA) detect IgM antibodies and are both useful for diagnosis early in the disease process. A persistently rising IgG complement fixation titer (1:16 or more) is suggestive of disseminated disease; in addition, immunodiffusion complement fixation titers can be used to assess the adequacy of therapy. Serum complement fixation titers may be low when there is meningitis but no other disseminated disease. In patients with HIV-related coccidioidomycosis, the false-negative rate may be as high as 30%. Blood cultures are rarely positive.

Patients in whom coccidioidomycosis is diagnosed should undergo evaluation for meningeal involvement when CNS symptoms or neurologic signs are present. Spinal fluid findings include increased cell count with lymphocytosis and reduced glucose. Spinal fluid culture is positive in approximately 30% of meningitis cases. Demonstrable complement-fixing antibodies in spinal fluid are diagnostic of coccidioidal meningitis. These are found in over 90% of cases; *Coccidioides* antigen or (1,3)-beta-D-glucan testing may augment (not replace) CSF antibody testing.

C. Imaging

Radiographic findings vary, but patchy, nodular, and lobar upper lobe pulmonary infiltrates are most common. Hilar lymphadenopathy may be visible and is seen in localized disease; mediastinal lymphadenopathy suggests dissemination. There may be pleural effusions and lytic lesions in bone with accompanying complicated soft tissue collections.

► Treatment

General symptomatic therapy should be provided as needed for disease limited to the chest with no evidence of progression. Itraconazole (400 mg orally daily divided into two doses) or fluconazole (200–400 mg or higher orally once or twice daily) should be given for disease in the chest, bones, and soft tissues; however, therapy must be continued for 6 months or longer after the disease is inactive to prevent relapse (Table 36–1). Response to therapy

should be monitored by following the clinical response and progressive decrease in serum complement fixation titers.

For progressive pulmonary or extrapulmonary disease, liposomal amphotericin B intravenously should be given, although oral azoles may be used for mild cases. Duration of therapy is determined by a declining complement fixation titer and a favorable clinical response. For meningitis, treatment usually is with high-dose oral fluconazole (400–1200 mg/day), although lumbar or cisternal intrathecal administration of amphotericin B daily in increasing doses up to 1–1.5 mg/day is used initially by some experienced clinicians or in cases refractory to fluconazole. Systemic therapy with liposomal amphotericin B, 3–5 mg/kg/day intravenously, is usually given concurrently with intrathecal therapy, but is not sufficient alone for the treatment of meningeal disease. Once the patient is clinically stable, oral therapy with an azole, usually with fluconazole (400 mg daily) and given lifelong, is the recommended alternative to intrathecal amphotericin B therapy.

Surgical drainage is necessary for management of soft tissue abscesses, necrotic bone, and complicated pulmonary disease (eg, rupture of coccidioidal cavity).

► Prognosis

The prognosis for patients with limited disease is good. Serial complement fixation titers should be performed after therapy for patients with coccidioidomycosis; rising titers warrant reinstitution of therapy because relapse is likely. Late CNS complications of adequately treated meningitis include cerebral vasculitis with stroke and hydrocephalus that may require shunting. There may be a benefit from short-term systemic corticosteroids following cerebrovascular events associated with coccidioides meningitis. Disseminated and meningeal forms still have mortality rates exceeding 50% in the absence of therapy.

Kimes KE et al. Pulmonary coccidioidomycosis. Semin Respir Crit Care Med. 2020;41:42. [PMID: 32000283]

PNEUMOCYSTOSIS (*Pneumocystis jirovecii* Pneumonia)



ESSENTIALS OF DIAGNOSIS

- ▶ Fever, dyspnea, dry cough, hypoxia with exertion; often only slight lung physical findings.
- ▶ Chest radiograph: diffuse interstitial disease or normal.
- ▶ Detection of *P jirovecii* in sputum, bronchoalveolar lavage fluid, or lung tissue; PCR of bronchoalveolar lavage; (1,3)-beta-D-glucan in blood.

► General Considerations

Pneumocystis jirovecii, the *Pneumocystis* species that affects humans, is found worldwide.

The overt infection is a subacute interstitial pneumonia that occurs among older children and adults with abnormal or altered cellular immunity, either due to an underlying disease process (eg, cancer, malnutrition, stem cell or organ transplantation or, most commonly, AIDS) or due to treatment with immunosuppressive medications (eg, corticosteroids or cytotoxic agents).

Pneumocystis pneumonia occurs in up to 80% of AIDS patients not receiving prophylaxis and is a major cause of morbidity and mortality. Its incidence increases in direct proportion to the fall in CD4 cells, with most cases occurring at CD4 cell counts less than 200/mcL. In non-AIDS patients receiving immunosuppressive therapy, symptoms frequently begin after corticosteroids have been tapered or discontinued.

► Clinical Findings

A. Symptoms and Signs

Findings are usually limited to the pulmonary parenchyma. Onset may be subacute, characterized by dyspnea on exertion and nonproductive cough. Pulmonary physical findings may be slight and disproportionate to the degree of illness and the radiologic findings; some patients have bibasilar crackles. Without treatment, the course is usually one of rapid deterioration and death. Adult patients may present with spontaneous pneumothorax, usually in patients with previous episodes or those receiving aerosolized pentamidine prophylaxis. Patients with AIDS will usually have other evidence of HIV-associated disease, including fever, fatigue, and weight loss, for weeks or months preceding the illness.

B. Laboratory Findings

Arterial blood gas determinations usually show hypoxemia with hypocapnia but may be normal; however, rapid desaturation occurs if patients exercise before samples are drawn. Measurement of serum (1,3)-beta-D-glucan levels has good sensitivity, although specificity is compromised by being positive in other fungal infections. The organism cannot be cultured, and definitive diagnosis depends on morphologic demonstration of the organisms in respiratory specimens using specific stains, such as immunofluorescence. Polymerase chain reaction (PCR) of bronchoalveolar lavage is overly sensitive in that the test can be positive in colonized, uninfected persons; quantitative values may help with identifying infected patients, although precise cutoffs have not been established. A negative PCR from bronchoalveolar lavage rules out disease. Open lung biopsy and needle lung biopsy are infrequently required but may aid in diagnosing a granulomatous form of *Pneumocystis* pneumonia.

C. Imaging

Chest radiographs most often show diffuse “interstitial” infiltration, which may be heterogeneous, miliary, or patchy early in infection. There may also be diffuse or focal consolidation, cystic changes, nodules, or cavitation within nodules. About 5–10% of patients with *Pneumocystis* pneumonia have normal chest films. High-resolution chest CT scans may be quite suggestive of *P jirovecii* pneumonia, helping distinguish it from other causes of pneumonia.

► Treatment

It is appropriate to start empiric therapy for *P. jirovecii* pneumonia if the disease is suspected clinically; however, in both AIDS patients and non-AIDS patients with mild to moderately severe disease, continued treatment should be based on a proven diagnosis because of clinical overlap with other infections, the toxicity of therapy, and the possible coexistence of other infectious organisms. Oral trimethoprim-sulfamethoxazole (TMP-SMZ) is the preferred agent because of its low cost and excellent bioavailability; patients suffering from nausea and vomiting or intractable diarrhea should be given intravenous TMP-SMZ until they can tolerate the oral formulation. The best-studied second-line option is a combination of primaquine and clindamycin, although dapsone/trimethoprim, pentamidine, and atovaquone have been used. Therapy should be continued with the selected medication for at least 5–10 days before considering changing agents, as fever, tachypnea, and pulmonary infiltrates persist for 4–6 days after starting treatment. Some patients have a transient worsening of their disease during the first 3–5 days, which may be related to an inflammatory response secondary to the presence of dead or dying organisms. Early addition of corticosteroids may attenuate this response (see below).

A. Trimethoprim-Sulfamethoxazole

There are strong data indicating that TMP-SMZ is the optimal first-line therapy for *Pneumocystis* pneumonia. The dosage of TMP-SMZ is 15–20 mg/kg/day (based on trimethoprim component) given orally or intravenously daily in three or four divided doses for 14–21 days. Patients with AIDS have a high frequency of hypersensitivity reactions (approaching 50%), which may include fever, rashes (sometimes severe), malaise, neutropenia, hepatitis, nephritis, thrombocytopenia, hyperkalemia, and hyperbilirubinemia.

B. Primaquine/Clindamycin

A meta-analysis suggested that primaquine, 15–30 mg orally daily, plus clindamycin, 600 mg three times orally daily, is the best second-line therapy with superior results when compared with pentamidine. Primaquine may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

C. Pentamidine Isethionate

The use of pentamidine has decreased as alternative agents have been studied. This medication is administered intravenously (preferred) or intramuscularly as a single dose of 3–4 mg (salt)/kg/day for 14–21 days. Pentamidine causes side effects in nearly 50% of patients. Hypoglycemia (often clinically inapparent), hyperglycemia, hyponatremia, and delayed nephrotoxicity with azotemia may occur.

D. Atovaquone

Atovaquone is FDA approved for patients with mild to moderate disease who cannot tolerate TMP-SMZ or pentamidine, but failure is reported in 15–30% of cases. Mild side effects are common, but no serious reactions have

been reported. The dosage is 750 mg orally (taken with a fatty meal) two times daily for 21 days.

E. Other Medications

Trimethoprim, 15 mg/kg/day in three divided doses daily, plus dapsone, 100 mg/day, is an alternative oral regimen for mild to moderate disease or for continuation of therapy after intravenous therapy is no longer needed.

F. Prednisone

Based on studies done in patients with AIDS, prednisone is given for moderate to severe pneumonia (when PaO₂ on admission is less than 70 mm Hg or oxygen saturation is less than 90%) in conjunction with antimicrobials. The addition of corticosteroids in such patients is associated with significant reduction in morbidity and mortality; administration of adjunctive corticosteroids within 72 hours is preferred. The dosage of prednisone is 40 mg twice daily orally for 5 days, then 40 mg daily for 5 days, and then 20 mg daily until therapy is completed (total course, 21 days). Observational studies suggest that adjunctive corticosteroids are associated with reduced mortality in non-AIDS patients with *Pneumocystis* pneumonia and severe hypoxia (PaO₂ 60 mm Hg or less).

► Prevention

Primary prophylaxis for *Pneumocystis* pneumonia in HIV-infected patients should be given to persons with CD4 counts less than 200 cells/mcL. Primary prophylaxis is also beneficial in patients with hematologic malignancy and transplant recipients, and in patients receiving high-dose corticosteroid therapy, although precise recommendations for *Pneumocystis* prophylaxis in these settings have not been established. HIV-infected patients with a history of *Pneumocystis* pneumonia should receive secondary prophylaxis until they have had a durable virologic response to antiretroviral therapy and maintained a CD4 count of greater than 200 cells/mcL for at least 3–6 months.

► Prognosis

In the absence of early and adequate treatment, the fatality rate for *Pneumocystis* pneumonia in immunodeficient persons is nearly 100%. Early treatment reduces the mortality rate to ~10–20% in AIDS patients. The mortality rate in other immunodeficient patients is still 30–50%, probably because of failure to make a timely diagnosis. In immunodeficient patients who do not receive prophylaxis, recurrences are common (30% in AIDS).

Ding L et al. Adjunctive corticosteroids may be associated with better outcome for non-HIV *Pneumocystis* pneumonia with respiratory failure: a systemic review and meta-analysis of observational studies. Ann Intensive Care. 2020;10:34. [PMID: 32198645]

Stern A et al. Prophylaxis for *Pneumocystis* pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev. 2014;CD005590. [PMID: 25269391]

White PL et al. Therapy and management of *Pneumocystis jirovecii* infection. J Fungi (Basel). 2018;4:E127. [PMID: 30469526]

CRYPTOCOCCOSIS



ESSENTIALS OF DIAGNOSIS

- ▶ Most common cause of fungal meningitis.
- ▶ Predisposing factors: chemotherapy for hematologic malignancies, Hodgkin lymphoma, corticosteroid therapy, structural lung diseases, transplant recipients, TNF-alpha inhibitor therapy, and AIDS.
- ▶ Headache, abnormal mental status; meningismus seen occasionally, though rarely in patients with AIDS.
- ▶ Demonstration of capsular polysaccharide antigen or positive culture in CSF is diagnostic.

► General Considerations

Cryptococcosis is mainly caused by *Cryptococcus neoformans*, an encapsulated budding yeast that has been found worldwide in soil and on dried pigeon dung. *Cryptococcus gattii* is a closely related species that also causes disease in humans, although *C gattii* may affect more ostensibly immunocompetent persons. It is a major cause of cryptococcosis in the Pacific northwestern region of the United States and may result in more severe disease than *C neoformans*.

Infections are acquired by inhalation. In the lung, the infection may remain localized, heal, or disseminate. Clinically apparent cryptococcal pneumonia rarely develops in immunocompetent persons. Progressive lung disease and dissemination most often occur in the setting of cellular immunodeficiency, including hematologic malignancies under treatment, Hodgkin lymphoma, long-term corticosteroid therapy, solid-organ transplant, TNF-alpha inhibitor therapy, or HIV infection.

► Clinical Findings

A. Symptoms and Signs

Pulmonary disease ranges from simple nodules to widespread infiltrates leading to respiratory failure. Disseminated disease may involve any organ, but CNS disease predominates. Headache is usually the first symptom of meningitis. Confusion and other mental status changes as well as cranial nerve abnormalities, nausea, and vomiting may be seen as the disease progresses. Nuchal rigidity and meningeal signs occur about 50% of the time but are uncommon in patients with AIDS. Communicating hydrocephalus may complicate the course. *C gattii* infection frequently presents with respiratory symptoms along with neurologic signs caused by space-occupying lesions in the CNS. Primary *C neoformans* infection of the skin may mimic bacterial cellulitis, especially in persons receiving immunosuppressive therapy such as corticosteroids. The immune reconstitution inflammatory syndrome (IRIS), which is paradoxical clinical worsening associated with improved immunologic status, can occur in HIV-positive and transplant patients with cryptococcosis, as well as non-AIDS patients being treated for *C gattii* infection.

B. Laboratory Findings

Respiratory tract disease is diagnosed by culture of respiratory secretions or pleural fluid. For suspected meningeal disease, lumbar puncture is the preferred diagnostic procedure. Spinal fluid findings include increased opening pressure, variable pleocytosis, increased protein, and decreased glucose, though as many as 50% of AIDS patients have no pleocytosis. Gram stain of the CSF usually reveals budding, encapsulated fungi. In patients with AIDS, the serum cryptococcal antigen is a sensitive screening test for meningitis, being positive in over 95% of cases. Cryptococcal capsular antigen in CSF and culture together establish the diagnosis over 90% of the time. Antigen testing by lateral flow assay has improved sensitivity and specificity over the conventional latex agglutination test and can provide more rapid diagnostic results. MRI is more sensitive than CT in finding CNS abnormalities, such as cryptococcomas.

► Treatment

Because of decreased efficacy, initial therapy with an azole alone is not recommended for treatment of acute cryptococcal meningitis. Liposomal amphotericin B, 3–4 mg/kg/day intravenously for 14 days, is the preferred agent for **induction therapy**, followed by an additional 8 weeks of fluconazole, 400 mg/day orally for **consolidation** (Table 36–1). This regimen is quite effective, achieving clinical responses and CSF sterilization in over 70% of patients. The addition of flucytosine has been associated with improved survival, but toxicity is common. Flucytosine is administered orally at a dose of 100 mg/kg/day divided into four equal doses and given every 6 hours. Hematologic parameters should be closely monitored during flucytosine therapy, and it is important to adjust the dose for any decreases in kidney function. Fluconazole (800–1200 mg orally daily) may be given with amphotericin B when flucytosine is not available or patients cannot tolerate it. Frequent, repeated lumbar punctures or ventricular shunting should be performed to relieve high CSF pressures or if hydrocephalus is a complication. Corticosteroids should not be used. *Failure to adequately relieve raised intracranial pressure is a major cause of morbidity and mortality.* The end points for amphotericin B therapy and for switching to **maintenance** with oral fluconazole are a favorable clinical response (decrease in temperature; improvement in headache, nausea, vomiting, and Mini-Mental State Examination scores), improvement in CSF biochemical parameters and, most importantly, conversion of CSF culture to negative.

A similar approach is reasonable for patients with cryptococcal meningitis in the absence of AIDS, though the mortality rate is higher. Therapy is generally continued until CSF cultures become negative. **Maintenance** antifungal therapy is important after treatment of an acute episode in AIDS-related cases, since otherwise the rate of relapse is greater than 50%. Fluconazole, 200 mg/day orally, is the maintenance therapy of choice, decreasing the relapse rate approximately tenfold compared with placebo and threefold compared with weekly amphotericin B in patients whose CSF has been sterilized by the induction therapy.

After successful therapy of cryptococcal meningitis, it is possible to discontinue secondary prophylaxis with fluconazole in individuals with AIDS who have had a satisfactory response to antiretroviral therapy (eg, CD4 cell count greater than 100–200 cells/mcL for at least 6 months). Published guidelines suggest that 6–12 months of fluconazole can be used as maintenance therapy in patients without AIDS following successful treatment of the acute illness.

► Prognosis

Factors that indicate a poor prognosis include the activity of the predisposing conditions, older age, organ failure, lack of spinal fluid pleocytosis, high initial antigen titer in either serum or CSF, decreased mental status, increased intracranial pressure, and the presence of disease outside the nervous system.

Beardsley J et al. Central nervous system cryptococcal infections in non-HIV infected patients. *J Fungi (Basel)*. 2019;5:E71. [PMID: 31382367]

Zavala S et al. Cryptococcosis. *Semin Respir Crit Care Med*. 2020;41:69. [PMID: 32000285]

2. Chronic aspergillosis—Chronic pulmonary aspergillosis produces a spectrum of disease that usually occurs when there is preexisting lung damage but not significant immunocompromise. Disease manifestations range from aspergillomas that develop in a lung cavity to chronic fibrosing pulmonary aspergillosis in which the majority of lung tissue is replaced with fibrosis. Long-standing (longer than 3 months) pulmonary and systemic symptoms such as cough, shortness of breath, weight loss, and malaise are common.

3. Invasive aspergillosis—Invasive aspergillosis most commonly occurs in profoundly immunodeficient patients, such as those who have undergone hematopoietic stem cell transplantation or have prolonged, severe neutropenia, but it can occur among critically ill immunocompetent patients as well. Pulmonary aspergillosis has been observed in severe COVID-19 infection. Pulmonary disease is most common, with patchy infiltration leading to a severe necrotizing pneumonia. Invasive sinus disease also occurs. At any time, there may be hematogenous dissemination to the CNS, skin, and other organs. Early diagnosis and reversal of any correctable immunosuppression are essential.

B. Laboratory Findings

In ABPA, there is eosinophilia with high levels of IgE and IgG *Aspergillus* precipitins in the blood.

For invasive aspergillosis, definitive diagnosis requires demonstration of *Aspergillus* in tissue or culture from a sterile site; however, given the morbidity of the disease and the low yield of culture, clinicians must maintain a high index of suspicion and use a combination of host, radiologic, and mycologic criteria to yield a probable diagnosis of invasive aspergillosis in at-risk patients. Indirect diagnostic assays include detection of galactomannan in bronchoalveolar lavage fluid or serum or serum assays for (1,3)-beta-D-glucan (though the latter is not specific for *Aspergillus*); the diagnostic utility of *Aspergillus* DNA by PCR is debated. To improve the reliability of galactomannan testing, multiple determinations should be done, though sensitivity is decreased in patients receiving anti-mold prophylaxis (ie, voriconazole or posaconazole). Isolation of *Aspergillus* from pulmonary secretions does not necessarily imply invasive disease, although its positive predictive value increases with more advanced immunosuppression. Clinical suspicion for invasive aspergillosis should prompt CT scanning of the chest, which may aid in early detection and help direct additional diagnostic procedures. Common radiologic findings include nodules; wedge-shaped infarcts; or a characteristic “halo sign,” a zone of diminution of ground glass around a consolidation.

► Prevention

The high mortality rate and difficulty in diagnosis of invasive aspergillosis often lead clinicians to institute prophylactic therapy for patients with profound immunosuppression. The best-studied agents include posaconazole (300 mg orally daily) and voriconazole (200 mg orally twice daily), although patient and agent selection criteria remain

ASPERGILLOSIS

ESSENTIALS OF DIAGNOSIS

- ▶ Most common cause of non-candidal invasive fungal infection in transplant recipients and in patients with hematologic malignancies.
- ▶ Risk factors for invasive disease: leukemia, bone marrow or organ transplantation, corticosteroid use, advanced AIDS.
- ▶ Pulmonary, sinus, and CNS are most common disease sites.
- ▶ Detection of galactomannan in serum or other body fluids is useful for early diagnosis in at-risk patients.

► General Considerations

Aspergillus fumigatus is the usual cause of aspergillosis, though many species of *Aspergillus* may cause a wide spectrum of disease. The lungs, sinuses, and brain are the organs most often involved. Clinical illness results either from an aberrant immunologic response or tissue invasion.

► Clinical Findings

A. Symptoms and Signs

1. Allergic forms of aspergillosis—Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with pre-existing asthma or cystic fibrosis. Patients develop worsening bronchospasm and fleeting pulmonary infiltrates. Allergic aspergillus sinusitis produces a chronic sinus inflammation characterized by eosinophilic mucus and noninvasive hyphal elements.

undefined. Widespread use of broad-spectrum azoles raises concern for development of breakthrough invasive disease by highly resistant fungi.

► Treatment

1. Allergic forms of aspergillosis—Itraconazole is the best studied agent for the treatment of allergic aspergillus sinusitis with topical corticosteroids being the cornerstone of therapy for ongoing care. For acute exacerbations of ABPA, oral prednisone is begun at a dose of 0.5 mg/kg/day and then tapered slowly over several months. Itraconazole at a dose of 200 mg orally daily for 16 weeks appears to improve pulmonary function and decrease corticosteroid requirements in these patients; voriconazole is an alternative agent.

2. Chronic aspergillosis—The most effective therapy for symptomatic aspergilloma is surgical resection. Other forms of chronic aspergillosis are generally treated with at least 4–6 months of oral azole therapy (itraconazole 200 mg twice daily, voriconazole 200 mg twice daily, or posaconazole 300 mg daily); observational data suggest voriconazole may be superior to itraconazole for maintenance therapy.

3. Invasive aspergillosis—The 2016 Infectious Diseases Society of America guidelines consider voriconazole (6 mg/kg intravenously twice on day 1 and then 4 mg/kg every 12 hours thereafter) as optimal therapy for invasive aspergillosis. However, the 2017 European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology, and the European Respiratory Society (ESCMID-ECMM-ERS) joint clinical guidelines indicate either isavuconazole (200 mg intravenously every 8 hours for six doses, then 200 mg daily) or voriconazole as first-line therapy. Other alternatives include a lipid formulation of amphotericin B (3–5 mg/kg/day), caspofungin (70 mg intravenously on day 1, then 50 mg/day thereafter), micafungin (100–150 mg intravenously daily), and posaconazole oral tablets (300 mg twice daily on day 1, then 300 mg daily thereafter).

Treatment duration may vary depending on the clinical response but 6–12 weeks is generally recommended. Antifungal susceptibility testing of *Aspergillus* isolates is recommended in patients who are unresponsive to therapy or with clinical suspicion for azole resistance. Therapeutic drug monitoring should be considered for both voriconazole and posaconazole given variations in metabolism and absorption.

Surgical debridement is generally done for sinusitis, and can be useful for focal pulmonary lesions, especially for treatment of life-threatening hemoptysis and infections recalcitrant to medical therapy. The mortality rate of pulmonary or disseminated disease in the immunocompromised patient remains high, particularly in patients with refractory neutropenia.

Koehler P et al. COVID-19 associated pulmonary aspergillosis. *Mycoses*. 2020;63:528. [PMID: 32339350]

Russo A et al. Pulmonary aspergillosis: an evolving challenge for diagnosis and treatment. *Infect Dis Ther*. 2020;9:511. [PMID: 32638227]

Ullmann AJ et al. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect*. 2018;24:e1. [PMID: 29544767]

MUCORMYCOSIS

► ESSENTIALS OF DIAGNOSIS

- ▶ Most common cause of non-*Aspergillus* invasive mold infection.
- ▶ Risk factors: uncontrolled diabetes, leukemia, transplant recipient, wound contamination by soil.
- ▶ Pulmonary, rhinocerebral, and skin are most common disease sites.
- ▶ Rapidly fatal without multidisciplinary interventions.

► General Considerations

The term “mucormycosis” is applied to opportunistic infections caused by members of the genera *Rhizopus*, *Mucor*, *Lichtheimia* (formerly *Absidia*), and *Cunninghamella*. Predisposing conditions include hematologic malignancy; stem cell transplantation; solid organ transplantation; diabetic ketoacidosis; chronic kidney disease; and treatment with desferoxamine, corticosteroids, or cytotoxic drugs.

► Clinical Findings

Invasive disease of the sinuses, orbits, and the lungs may occur. Necrosis is common due to hyphal tissue invasion that may manifest as ulceration of the hard palate, nasal palate, or hemoptysis. Widely disseminated disease can occur. Biopsy of involved tissue remains the cornerstone of diagnosis; the organisms appear in tissues as broad, branching nonseptate hyphae. Cultures are frequently negative.

► Treatment

Optimal therapy of mucormycosis involves reversal of predisposing conditions (if possible), surgical debridement, and prompt antifungal therapy. A prolonged course of a lipid preparation of intravenous liposomal amphotericin B (5–10 mg/kg with higher doses given for CNS disease) should be started early. Oral posaconazole (300 mg/day) or isavuconazole (200 mg every 8 hours for 1–2 days, then 200 mg daily thereafter) can be used for less severe disease, as step-down therapy after disease stabilization, or as salvage therapy due to poor response to or tolerance of amphotericin. Combination therapy with amphotericin and posaconazole or isavuconazole is not proven but is commonly used because of the poor response to monotherapy. Control of diabetes and other underlying conditions, along

with extensive repeated surgical removal of necrotic, nonperfused tissue, is essential. Even when these measures are introduced in a timely fashion, the prognosis remains guarded.

Schwartz IS et al. Blastomycosis. *Semin Respir Crit Care Med.* 2020;41:31. [PMID: 32000282]

Brunet K et al. Mucormycosis treatment: recommendations, latest advances, and perspectives. *J Mycol Med.* 2020;30:101007. [PMID: 32718789]

Cornely OA et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis.* 2019;19:e405. [PMID: 31699664]

Lionakis MS et al. Breakthrough invasive mold infections in the hematology patient: current concepts and future directions. *Clin Infect Dis.* 2018;67:1621. [PMID: 29860307]

BLASTOMYCOSIS

Blastomycosis occurs most often in men infected during occupational or recreational activities outdoors and in a geographically limited area of the south, central, and midwestern United States and Canada. Disease usually occurs in immunocompetent individuals.

Pulmonary infection is most common and may be asymptomatic. With dissemination, lesions most frequently occur in the skin, bones, and urogenital system.

Cough, moderate fever, dyspnea, and chest pain are common. These may resolve or progress, with purulent sputum production, pleurisy, fever, chills, loss of weight, and prostration. Radiologic studies, either chest radiographs or CT scans, usually reveal lobar consolidation or masses.

Raised, verrucous cutaneous lesions are commonly present in disseminated blastomycosis. Bones—often the ribs and vertebrae—are frequently involved. Epididymitis, prostatitis, and other involvement of the male urogenital system may occur. Although they do not appear to be at greater risk for acquisition of disease, infection in HIV-infected persons may progress rapidly, with dissemination common.

Laboratory findings usually include leukocytosis and anemia. The organism is found in clinical specimens, such as expectorated sputum or tissue biopsies, as a 5–20 μm thick-walled cell with a single broad-based bud. It grows readily on culture. A urinary antigen test is available, but it has considerable cross reactivity with other dimorphic fungi; it may be useful in monitoring disease resolution or progression. The quantitative antigen enzyme immunoassay may be helpful in the diagnosis of CNS disease. A serum enzyme immunoassay based on the surface protein BAD-1 appears to have much better sensitivity and specificity than the urinary antigen test.

Itraconazole, 200–400 mg/day orally for at least 6–12 months, is the therapy of choice for nonmeningeal disease, with a response rate of over 80% (Table 36–1). Liposomal amphotericin B, 3–5 mg/kg/day intravenously, is given initially for severe disease, treatment failures, or CNS involvement.

Clinical follow-up for relapse should be made regularly for several years so that therapy may be resumed or another drug instituted.

SPOROTRICHOSIS

Sporotrichosis is a chronic fungal infection caused by organisms of the *Sporothrix schenckii* complex. It is worldwide in distribution; most patients have had contact with soil, sphagnum moss, or decaying wood. Infection takes place when the organism is inoculated into the skin—usually on the hand, arm, or foot, especially during gardening, or puncture from a rose thorn.

The most common form of sporotrichosis begins with a hard, nontender subcutaneous nodule. This later becomes adherent to the overlying skin and ulcerates. Within a few days to weeks, lymphocutaneous spread along the lymphatics draining this area occurs, which may result in ulceration. Cavitary pulmonary disease occurs in individuals with underlying chronic lung disease.

Disseminated sporotrichosis is rare in immunocompetent persons but may present with widespread cutaneous, lung, bone, joint, and CNS involvement in immunocompromised patients, especially those with cellular immunodeficiencies, including AIDS and alcohol abuse.

Cultures are needed to establish diagnosis. The usefulness of serologic tests is limited, but may be helpful in diagnosing disseminated disease, especially meningitis.

Itraconazole, 200–400 mg orally daily for several months, is the treatment of choice for localized disease and some milder cases of disseminated disease (Table 36–1). Terbinafine, 500 mg orally twice daily, also has good efficacy in lymphocutaneous disease. Amphotericin B intravenously, 0.7–1.0 mg/kg/day, or a lipid amphotericin B preparation, 3–5 mg/kg/day, is used for severe systemic infection. Surgery may be indicated for complicated pulmonary cavitary disease, and joint involvement may require arthrodesis.

The prognosis is good for lymphocutaneous sporotrichosis; pulmonary, joint, and disseminated disease respond less favorably.

Orofino-Costa R et al. Sporotrichosis: an update on epidemiology, etiopathogenesis, laboratory and clinical therapeutics. *An Bras Dermatol.* 2017;92:606. [PMID: 29166494]

MYCETOMA (EUMYCETOMA & ACTINOMYCETOMA)

Mycetoma is a chronic local, slowly progressive destructive infection that usually involves the foot; it begins in subcutaneous tissues, frequently after implantation of vegetative material into tissues during occupational activities. The infection then spreads to contiguous structures with sinus tracts and extruding grains. Eumycetoma (also known as maduromycosis) is the term used to describe mycetoma caused by true fungi. The disease begins as a papule, nodule, or abscess that over months to years progresses slowly to form multiple abscesses and sinus tracts ramifying deep into the tissue. Secondary bacterial infection may result in large open ulcers. Radiographs may show destructive changes in the underlying bone. Causative species can

often be suggested by the color of the characteristic grains and hyphal size within the infected tissues but definitive diagnosis requires culture.

The prognosis for eumycetoma is poor, though surgical debridement along with prolonged oral itraconazole therapy, 200 mg twice daily, or combination therapy including itraconazole and terbinafine may result in a response rate of 70% (Table 36–1). The various etiologic agents may respond differently to antifungal agents, so culture results are invaluable. Amputation is necessary in far advanced cases.

van de Sande W et al. Closing the mycetoma knowledge gap. *Med Mycol*. 2018;56:153. [PMID: 28992217]

OTHER OPPORTUNISTIC MOLD INFECTIONS

Fungi previously considered to be harmless colonizers, including *Pseudallescheria boydii* (*Scedosporium apiospermum*), *Scedosporium prolificans*, *Fusarium*, *Paecilomyces*, *Trichoderma longibrachiatum*, and *Trichosporon*, are now significant pathogens in immunocompromised patients. Opportunistic infections with these agents are seen in patients being treated for hematologic malignancies, in stem cell or organ transplant recipients, and in those receiving broad-spectrum antifungal prophylaxis. Infection may be localized in the skin, lungs, or sinuses, or widespread disease may appear with lesions in multiple organs. Fusariosis should be suspected in severely immunosuppressed persons in whom multiple, painful skin lesions develop; blood cultures are often positive. Sinus infection may cause bony erosion. Infection in subcutaneous tissues following traumatic implantation may develop as a well-circumscribed cyst or as an ulcer.

Nonpigmented septate hyphae are seen in tissue and are indistinguishable from those of *Aspergillus* when infections are due to *S apiospermum* or species of *Fusarium*, *Paecilomyces*, *Penicillium*, or other hyaline molds. The differentiation of *S apiospermum* and *Aspergillus* is particularly important, since the former is uniformly resistant to amphotericin B but may be sensitive to azole antifungals (eg, voriconazole). Treatment of fusariosis may include amphotericin, voriconazole, or combination therapy; there are limited data on the use of isavuconazole or posaconazole for this disease. In addition to antifungal therapy, reversal of underlying immunosuppression is an essential component of treatment for these invasive mold infections.

Infection by any of a number of black molds is designated as phaeohyphomycosis. These black molds (eg, *Exophiala*, *Bipolaris*, *Cladophialophora*, *Curvularia*, *Alternaria*) are common in the environment, especially on decaying vegetation. In tissues of patients with phaeohyphomycosis, the mold is seen as black or faintly brown hyphae, yeast cells, or both. Culture on appropriate medium is needed to identify the agent. Histologic demonstration of these organisms is definitive evidence of invasive infection; positive cultures must be interpreted cautiously and not assumed to be contaminants in immunocompromised hosts.

Arcobello JT et al. Phaeohyphomycosis. *Semin Respir Crit Care Med*. 2020;41:131. [PMID: 32000289]

HOUSEHOLD MOLDS



ESSENTIALS OF DIAGNOSIS

- Molds are very common indoors where moisture exists in enclosed spaces.
- Most common indoor molds are *Cladosporium*, *Penicillium*, *Aspergillus*, and *Alternaria*.
- People most at risk for health problems include those with allergies, asthma, and underlying immunocompromising conditions.

Molds are commonly present in homes, particularly in the presence of moisture, and patients will commonly seek assessment for whether their illness is due to molds. Well-established health problems due to molds can be considered in three categories: (1) There is the potential for allergy to environmental mold species, which can manifest in the typical manner with allergic symptoms such as rhinitis and eye irritation. Furthermore, in predisposed individuals, exposure to certain molds can trigger asthma or asthmatic attacks. These types of manifestations are reversible with appropriate therapies. More chronic allergic effects can be seen with disorders such as allergic bronchopulmonary aspergillosis (see Allergic Forms of Aspergillosis); (2) Susceptible individuals can develop hypersensitivity reactions upon exposure to mold antigens; these include occupational disorders (eg, farmer's lung and pigeon breeder's disease) as well as hypersensitivity pneumonitis in response to a large antigenic exposure. Affected patients have fever, lymph node swelling, and pulmonary infiltrates. These disease manifestations are transient and improve with removal of the offending antigen; (3) Invasive mold disease (see Invasive Aspergillosis).

At the present time, there are no data to support that mold exposure can induce immune dysfunction. Similarly, the concept of toxic-mold syndrome or cognitive impairment due to inhalation of mycotoxins has not been validated despite scrutiny by expert panels. The presence of mold in the household is typically easily discernable with visual inspection or detection by odor; if present, predisposing conditions should be corrected by individuals experienced in mold remediation.

A number of laboratories offer testing for the evaluation of patients who suspect they have a mold-induced disorder, such as testing homes for mold spores, measuring urinary "mycotoxins," and performing serum IgG assays to molds. However, these tests should not be obtained as most are not validated and do not provide meaningful results upon which to make therapeutic decisions.

Borchers AT et al. Mold and human health: a reality check. *Clin Rev Allergy Immunol*. 2017;52:305. [PMID: 28299723]
 Chang C et al. The myth of mycotoxins and mold injury. *Clin Rev Allergy Immunol*. 2019;57:449. [PMID: 31608429]

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Disorders Related to Environmental Emergencies

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COLD & HEAT

The human body maintains a steady temperature through the balance of internal heat production and environmental heat loss. Heat exchange between the body and environment occurs via four common processes: radiation, evaporation, conduction, and convection. In extreme temperatures, the body's thermoregulation may fail, resulting in the core body temperature moving toward the temperature of the external environment. Cold and heat exposure may cause a wide spectrum of conditions ranging in severity from mild to potentially life threatening to death. Many of these conditions are preventable with appropriate education and planning.

The likelihood and severity of extreme temperature-related conditions depend on physiologic and environmental factors. Physiologic risk factors include extremes of age; cognitive impairment; poor physical conditioning, sedentary lifestyle, or immobility; poor acclimatization; concurrent injury; prior temperature-related injury; and numerous underlying medical conditions, especially those affecting cognition and thermoregulation. Pharmacologic risk factors include medications, holistic or alternative treatments, illicit drugs, tobacco, and alcohol. Medications impacting sweating and the central nervous system, or affecting cutaneous blood flow, such as peripheral vasoconstrictors or vasodilators, are more likely to worsen temperature-related conditions. Environmental risk factors include changing weather conditions, inadequate clothing or housing (homelessness, or housing with inadequate temperature control), and occupational or recreational exposure.

DISORDERS DUE TO HEAT



ESSENTIALS OF DIAGNOSIS

- ▶ Spectrum of preventable heat-related illnesses: heat cramps, heat exhaustion, heat syncope, and heat stroke.
- ▶ **Heat stroke:** hyperthermia with cerebral dysfunction in a patient with heat exposure.

- ▶ **Best outcome:** early recognition, initiation of rapid cooling, and avoidance of shivering during cooling; delays in cooling result in higher morbidity and mortality in heat stroke victims.
- ▶ **Best choice of cooling method:** whichever can be instituted the fastest with the least compromise to the patient.

► General Considerations

Heat-related illnesses are among the most commonly seen environmental emergencies presenting to emergency departments. The amount of heat retained in the body is determined by internal metabolic function and environmental conditions, including temperature and humidity. Hyperthermia results from the body's inability to maintain normal internal temperature through heat loss. Hyperthermia results from either compromised heat dissipation mechanisms or abnormally high heat production. Increased metabolic rate is the most important factor in elevation of body temperature. Heat loss occurs primarily through sweating and peripheral vasodilation. The direct transfer of heat from the skin to the surrounding air, by convection or conduction, occurs with diminishing efficiency as ambient temperature rises, especially above 37.2°C (the point at which heat transfer reverses direction). At normal temperatures, evaporation accounts for approximately 20% of the body's heat loss, but at high temperatures it becomes the primary mechanism for dissipation of heat. This mechanism diminishes as humidity rises.

Heat stress can be caused by a combination of environmental and metabolic heat. Climate change may significantly contribute to the risk of heat-related conditions.

There is a spectrum of preventable heat stress conditions, ranging from mild forms, such as heat cramps, to severe forms, such as heat stroke. Risk factors include longer duration of exertion, hot environment, insufficient acclimatization, and dehydration. Additional risk factors include skin disorders or other medical conditions that inhibit sweat production or evaporation, obesity, prolonged seizures, hypotension, reduced cutaneous blood flow, reduced cardiac output, the use of drugs that increase

metabolism or muscle activity or impair sweating, and withdrawal syndromes. Illicit drugs can cause increased muscle activity and thus generate increased body heat.

Classic (nonexertional) heat-related illness may occur in any individual in a hot, relaxing environment with increased severity in individuals with the risk factors mentioned above, despite minimal physical activity.

Heat cramps are exercise-associated painful involuntary muscle contractions during or immediately after exercise. They result from dilutional hyponatremia as sweat losses are replaced with water alone. **Heat exhaustion** is characterized by dehydration, sodium depletion, or isotonic fluid loss with accompanying cardiovascular changes. It results from prolonged strenuous activity in a hot environment without adequate water or salt intake.

Heat syncope is defined as a transient loss of consciousness with spontaneous return to normal mentation. It results from volume depletion and cutaneous vasodilation with subsequent systemic and cerebral hypotension. Exercise-associated postural hypotension is usually the cause of heat syncope and may occur during or immediately following exercise. **Heat stroke** is a severe form of heat-related illness resulting in cerebral dysfunction with core body temperature over 40°C. It may present in one of two forms: classic and exertional. **Classic (nonexertional) heat stroke** occurs in patients with impaired thermoregulatory mechanisms or in extreme environmental conditions. **Exertional heat stroke** occurs in healthy persons undergoing strenuous exertion in a hot or humid environment. Persons at greatest risk are those who are at the extremes of age, chronically debilitated, and taking medications that interfere with heat-dissipating mechanisms.

► Clinical Findings

When diagnosing and treating heat-related illnesses, it is necessary to use an internal (rectal, Foley, or esophageal) thermometer since the skin temperature may not accurately reflect core body temperature. **Heat cramps** are painful skeletal muscle contractions and severe muscle spasms with onset during or shortly after exercise. Examination findings typically include stable vital signs; normal or slightly increased core body temperature; moist and cool skin; and tender, hard, lumpy, painful muscles that may be twitching. The diagnosis is made clinically.

Heat exhaustion is diagnosed based on symptoms and clinical findings of a core body temperature slightly elevated but less than 40°C, tachycardia, and moist skin. Symptoms are similar to those of heat cramps and heat syncope. Additional symptoms include nausea, vomiting, malaise, myalgias, hyperventilation, thirst, and weakness. Central nervous system symptoms include headache, dizziness, fatigue, anxiety, paresthesias, impaired judgment, and occasionally psychosis. Heat exhaustion may progress to heat stroke if sweating ceases and mental status declines.

Heat syncope generally occurs in the setting of prolonged vigorous physical activity or prolonged standing in a hot humid environment followed by a sudden collapse. Physical examination may reveal cool and moist skin, a weak pulse, and low systolic blood pressure.

Heat stroke is a life-threatening emergency. The hallmark of heat stroke is cerebral dysfunction when the core body temperature is over 40°C. Presenting symptoms include all findings seen in heat exhaustion with additional neurologic symptoms such as dizziness, weakness, emotional lability, confusion, delirium, blurred vision, convulsions, collapse, and unconsciousness. Physical examination findings may be variable and therefore unreliable. Exertional heat stroke may present with sudden collapse and loss of consciousness followed by irrational behavior. Sweating may not be present. Clinicians must be vigilant in monitoring for kidney injury, liver failure, metabolic derangements, respiratory compromise, coagulopathy, and ischemia, since initial laboratory findings may be nonspecific.

► Treatment

A. Heat Cramps

Move the patient to a shaded, cool environment and provide oral isotonic or hypertonic rehydration solution to replace both electrolytes and water. *Oral salt tablets are not recommended.* Advise the patient to rest for at least 2 days with continued dietary supplementation before returning to work or resuming strenuous activity in the heat.

B. Heat Exhaustion

Move the patient to a shaded, cool environment, provide adequate fluid and electrolyte replacement, and initiate active cooling measures if necessary. Physiologic saline or isotonic glucose solution may be administered intravenously when oral administration is not appropriate. At least 48 hours of rest and rehydration are recommended.

C. Heat Syncope

Treatment is essentially the same as for heat exhaustion: rest and recumbency in a shaded, cool place, and fluid and electrolyte replacement by mouth, or intravenously if necessary.

D. Heat Stroke

Initially, the patient's ABCs (airway, breathing, circulation) must be addressed and stabilized, then treatment is aimed at rapidly reducing the core body temperature within 1 hour while supporting circulation and perfusion. Patients should be placed on pulse oximetry and cardiac monitors while continuing to measure core body temperature and fluid intake and output. The patient should be observed for complications such as hypovolemic or cardiogenic shock, metabolic abnormalities, cardiac arrhythmias, coagulopathy, acute respiratory distress syndrome (ARDS), hypoglycemia, rhabdomyolysis, seizures, organ dysfunction, infection, and severe edema that can progress to a compartment syndrome. Circulatory failure in heat-related illness is mostly due to shock from relative or absolute hypovolemia. Oral or intravenous fluid administration must be provided to ensure adequate urinary output. Clinicians must also assess for and treat concurrent conditions such as infection, trauma, and drug effects.

Choice of cooling method depends on which can be instituted the fastest with the least compromise to the overall care of the patient. Evaporative cooling is preferred for nonexertional heat stroke and conductive-based cooling for exertional heat stroke. **Evaporative cooling** is a noninvasive, effective, quick, and easy way to reduce temperature. This is accomplished by placing the undressed patient in lateral recumbent position or supported in a hands-and-knees position to expose maximum skin surface to the air while the entire undressed body is sprayed with lukewarm water (20°C) and cooled by large fans circulating room air. Addition of inhaled cool air or oxygen may aid in cooling but must not be used alone. **Conductive-based cooling** involves cool fluid infusion, gastric or bladder lavage, ice packs, and immersion into ice water or cool water. When immersion in ice water or cold water is available in the field, it is the preferred method of cooling for exertional heat stroke. Ice packs are most effective when covering the whole body, as opposed to the traditional method of placing them in the axilla and groin only. Intravascular heat exchange catheter systems as well as hemodialysis using cold dialysate (30–35°C) have also been successful in reducing core body temperature.

Shivering must be avoided because it inhibits the effectiveness of cooling by increasing internal heat production. Medications can be used to suppress shivering including magnesium, quick-acting opioid analgesics, benzodiazepines, and quick-acting anesthetic agents. Skin massage is recommended to prevent cutaneous vasoconstriction. *Antipyretics (aspirin, acetaminophen) have no effect on environmentally induced hyperthermia and are contraindicated.* Treatment must be continued until the core body temperature drops to 39°C.

► Prevention

Education is necessary to improve prevention and early recognition of heat-related disorders. Individuals may take steps to reduce personal risk factors and to gradually acclimatize to hot environments. For prevention of occupational heat-related illness, a comprehensive preventive program should assess personal risk factors, estimated wet-bulb globe temperature, workload, acclimatization status, and early symptom recognition.

Coaches, athletic trainers, athletes, and parents of young athletes must be educated about heat-related illness, specifically about prevention, risks, symptoms and signs, and treatment. Medical evaluation and monitoring should be used to identify the individuals and the weather conditions that increase the risk of heat-related disorders.

Those who are physically active in a hot environment must increase fluid consumption before, during, and after physical activities. Fluid consumption should include balanced electrolyte fluids and water. Water consumption alone may lead to electrolyte imbalance, particularly hyponatremia. *It is not recommended to have salt tablets available for use because of the risk of hypertonic hyponatremia.* Close monitoring of fluid and electrolyte intake and early intervention are recommended in situations necessitating exertion or activity in hot environments.

► Prognosis

Mortality is high from heat stroke, most frequently secondary to multiorgan dysfunction. The patient is also at risk for rhabdomyolysis, ARDS, and inflammation even after core temperature has normalized. Following heat stroke, immediate reexposure to ambient heat must be avoided.

► When to Refer

Potential consultants include a surgeon for suspicion of compartment syndrome, nephrologist for kidney injury, and transplant surgeon for fulminant liver failure.

► When to Admit

All patients with suspected heat stroke must be admitted to a hospital with intensive care capability for close monitoring.

Epstein Y et al. Heatstroke. N Engl J Med. 2019;380:2449. [PMID: 31216400]

Gauer R et al. Heat-related illnesses. Am Fam Physician. 2019; 99:482. [PMID: 30990296]

King MA et al. Influence of prior illness on exertional heat stroke presentation and outcome. PLoS One. 2019;14:e0221329. [PMID: 31430332]

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ACCIDENTAL SYSTEMIC HYPOTHERMIA

ESSENTIALS OF DIAGNOSIS

- ▶ Systemic hypothermia is a core body temperature < 35°C.
- ▶ Accurate core body temperature measurement must be obtained using a low-reading core temperature probe that measures as low as 25°C.
- ▶ Core body temperature must be > 32°C before terminating resuscitation efforts.
- ▶ Extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass may be considered in hypothermic patients with hemodynamic instability or cardiac arrest.

► General Considerations

Systemic hypothermia is defined as core body temperature below 35°C. This may be primary, from exposure to prolonged ambient, extremely low temperature, or secondary, due to thermoregulatory dysfunction. Both may be present at the same time.

Hypothermia must be considered in any patient with prolonged exposure to an ambient cold environment, especially in any patients with prior cold weather injury as well as the risk factors listed in the Cold & Heat section. In prolonged or repetitive cold exposure, hypothermia ensues if the body's thermoregulatory responses become impaired.

Clinical Findings

Symptoms and signs of hypothermia are typically nonspecific and markedly variable based on the patient's underlying health and circumstances of cold exposure. Laboratory studies must assess acid-base status; electrolytes, particularly potassium and glucose; kidney, liver, and pancreas function; coagulation; and rhabdomyolysis. Inaccurate laboratory values will occur if the blood sample is warmed to 37°C for testing. All patients must be evaluated for associated conditions including hypoglycemia, trauma, infection, overdose, and peripheral cold injury.

Accurate core body temperature measurements must be obtained using a low-reading core temperature probe that measures as low as 25°C. **Stage I hypothermia** is typically seen when the core body temperature is between 32°C and 35°C and is defined by shivering and possibly poor judgment or coordination but with hemodynamic stability and a normal level of consciousness. **Stage II hypothermia** correlates with core body temperature 28–32°C. Shivering stops; bradycardia, dilated pupils, slowed reflexes, cold diuresis, and confusion and lethargy ensue. The electrocardiogram (ECG) may reveal a J wave or Osborn wave (positive deflection in the terminal portion of the QRS complex, most notable in leads II, V₅, and V₆) (Figure 37–1). When the core body temperature is below 28°C, the likelihood of hemodynamic instability and cardiac arrest increases dramatically. **Stage III hypothermia** (core body temperature 24–28°C) is characterized by loss of consciousness but present vital signs. **Stage IV hypothermia** (core body temperature less than 24°C) is the loss of vital signs. Coma, loss of reflexes, asystole, or ventricular fibrillation may falsely lead the clinician to assume the patient is dead despite reversible hypothermia.

Treatment

Rewarming is the initial, imperative treatment for all hypothermic patients. Resuscitation begins with rapid assessment

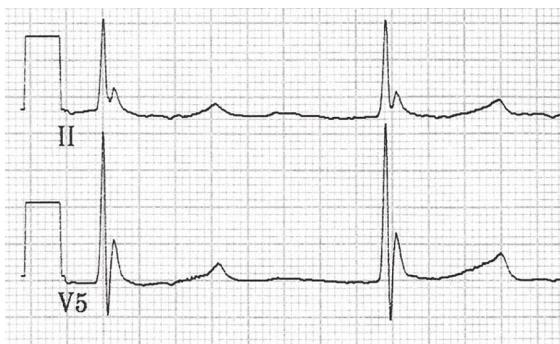


Figure 37–1. Electrocardiogram shows leads II and V₅ in a patient whose body temperature is 24°C. Note the bradycardia and Osborn waves. These findings become more prominent as the body temperature lowers and gradually resolve with rewarming. Osborn waves have an extra positive deflection in the terminal portion of the QRS complex and are best seen in the inferior and lateral precordial leads (most notably in leads II, V₅, and V₆).

and support of airway, breathing, and circulation, simultaneously with the initiation of rewarming, and prevention of further heat loss. All cold, wet clothing must be removed and replaced with warm, dry clothing and blankets.

Mild or stage I hypothermia can be treated with **passive external rewarming** (eg, removing and replacing wet clothes with dry ones) or by active external rewarming. In contrast to those with more severe hypothermia, it is safe and recommended for the uninjured patient with mild hypothermia to become physically active to generate heat.

Active external rewarming is noninvasive, highly effective, and safe for mild hypothermia. It involves applying external heat to the patient's skin. Examples include warm bedding, heated blankets, heat packs, and immersion into a 40°C bath. Warm bath immersion limits the ability to monitor the patient or treat other coexisting conditions. Patients with mild hypothermia and previous good health usually respond well to passive and active external warming.

Stage II and III hypothermia are treated as above with the addition of more aggressive rewarming strategies. This requires close monitoring of vital signs and cardiac rhythm during rewarming. Warm intravenous fluids (38–42°C) are considered minimally invasive and effective.

As hypothermia becomes more severe, there are increased complications of both hypothermia itself and of rewarming. Complications of rewarming occur as colder peripheral blood returns to central circulation. This may result in core temperature afterdrop, rewarming lactic acidosis from shunting lactate into the circulation, rewarming shock from peripheral vasodilation, and hypovolemia, ventricular fibrillation, and other cardiac arrhythmias. Afterdrop can be lessened by active external rewarming of the trunk but not the extremities and by avoiding any muscle movement by the patient. Extreme caution must be taken when handling the hypothermic patient to avoid triggering potentially fatal arrhythmias in a phenomenon known as rescue collapse.

Patients with hemodynamic instability or cardiac arrest should be transferred to a facility with ECMO or cardio-pulmonary bypass capability.

Early recognition and advanced management guidelines are needed for patients with stage IV hypothermia. For hypothermic patients in cardiac arrest, high-quality CPR must be initiated and continued until the patient's core body temperature is at least 32°C. Below 30°C, arrhythmias and asystole may be refractory to drug therapy until the patient has been rewarmed; therefore, treatment should focus on excellent CPR technique in conjunction with aggressive rewarming of the patient. Epinephrine or vasopressin may be given in cardiac arrest of the severely hypothermic patient. International Commission for Mountain Emergency Medicine recommends extracorporeal life support as the treatment of choice for patients at high risk for hypothermic cardiac arrest. Extracorporeal life support has been shown to substantially improve survival of patients with unstable circulation or cardiac arrest.

Any hypothermic patient with return of spontaneous circulation must be monitored very closely because of the high likelihood of subsequent multiorgan system failure.

► When to Admit

Hypothermia patients must undergo close monitoring for potential complications. This is typically done during an inpatient admission or prolonged emergency department observation.

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Pasquier M et al. An evaluation of the Swiss staging model for hypothermia using hospital cases and case reports from the literature. *Scand J Trauma Resusc Emerg Med*. 2019;27:60. [PMID: 31171019]

HYPOTHERMIA OF THE EXTREMITIES



ESSENTIALS OF DIAGNOSIS

- ▶ "Keep warm, keep dry, and keep moving" to prevent cold-induced injury.
- ▶ Rewarming of the extremity suffering cold-induced injury must be performed as soon as possible once there is no risk of refreezing; exercise, rubbing, or massage must be avoided during rewarming.

► Clinical Findings

Cold exposure of the extremities produces immediate localized and then generalized vasoconstriction, which may result in a wide range of injuries. Tissue damage occurs because of ischemia and intravascular thromboses, endothelial damage, or actual freezing. Freezing (frostbite) may occur when skin temperatures drop or in the presence of wind, water, immobility, malnutrition, or vascular disease.

For all forms of cold-induced injury to an extremity, caution must be taken to avoid rubbing or massaging the injured area and to avoid applying moisture, ice, or heat. The cold-injured extremity must be protected from trauma, secondary infection, and further cold exposure.

► Prevention

"Keep warm, keep dry, and keep moving." For optimal prevention of frostbite, individuals must wear warm, dry clothing. Arms, legs, fingers, and toes must be exercised to maintain circulation. Wet clothing, socks, and shoes must be replaced with dry ones. Risk factors include underlying diseases or medications that decrease tissue perfusion and prolonged cold environmental exposure. Caution must be taken to avoid cramped positions; wet or constrictive

clothing; prolonged dependency of the feet; use of tobacco, alcohol, and sedative medications; and exposure to wet, muddy ground and windy conditions.

FROSTNIP & CHILBLAIN (Erythema Pernio)

Frostnip is a superficial nonfreezing injury causing local paresthesias of the involved area that completely resolves with passive external rewarming.

Chilblains, or **erythema pernio**, are inflammatory skin changes caused by exposure to cold without actual freezing of the tissues. These skin lesions may be red or purple papular lesions, which are painful or pruritic, with burning or paresthesias. They may be associated with edema or blistering and aggravated by warmth. With continued exposure, ulcerative or hemorrhagic lesions may appear and progress to scarring, fibrosis, and atrophy. Treatment consists of elevating and passively externally rewarming the affected part.

IMMERSION FOOT OR TRENCH FOOT

Immersion foot (or hand) is caused by prolonged immersion in cold water or mud, usually below 10°C. **Prehyperemic stage** is marked by early symptoms of cold and anesthesia of the affected area. **Hyperemic stage** follows with a hot sensation, intense burning, and shooting pains. **Posthyperemic stage** occurs with ongoing cold exposure; the affected part becomes pale or cyanotic with diminished pulsations due to vasospasm. This may result in blistering, swelling, redness, ecchymoses, hemorrhage, necrosis, peripheral nerve injury, or gangrene.

Treatment consists of air drying and gradual rewarming by exposure to air at room temperature. Affected parts are elevated to aid in removal of edema fluid. Pressure sites are protected with cushions. Bed rest is required until all ulcers have healed.

FROSTBITE

Frostbite is injury from tissue freezing and formation of ice crystals in the tissue. Most tissue destruction follows reperfusion of the frozen tissues resulting in further tissue damage. In mild cases, only the skin and subcutaneous tissues are involved. Symptoms include numbness, prickling, itching, and pallor. With increasing severity, deeper structures become involved; the skin appears white or yellow, loses elasticity, and becomes immobile. Edema, hemorrhagic blisters, necrosis, gangrene, paresthesias, and stiffness may occur.

► Treatment

A. Immediate Treatment

Evaluate and treat the patient for associated systemic hypothermia, concurrent conditions, and injury. Early use of systemic analgesics is recommended for nonfrozen

injuries. Hydrate the patient to avoid hypovolemia and to improve perfusion.

1. Rewarming—Rapid rewarming at temperatures slightly above normal body temperature may significantly decrease tissue necrosis and reverse the tissue crystallization. **If there is any possibility of refreezing, the frostbitten part must not be thawed.** Ideally, the frozen extremity must not be used, but if required for evacuation, the affected frozen extremity must be padded and splinted to avoid additional injury. Rewarming is best accomplished by warm bath immersion. The frozen extremity is immersed in a moving water bath heated to 37–39°C for approximately 30 minutes until the area becomes soft and pliable to the touch. Water in this temperature range feels warm but not hot to the normal hand or wrist. If warm water is not available, then passive thawing in a warm environment must be allowed. Dry heat is not recommended because it is more difficult to regulate and increases the likelihood of accidental burns. Thawing may cause tenderness and burning pain. Once the frozen part has thawed and returned to normal temperature, discontinue external heat. **In the early stage, rewarming by exercise, rubbing, or friction is contraindicated.** The patient must be kept on bed rest with the affected parts elevated and uncovered at room temperature. Avoid application of casts, occlusive dressings, or bandages. Blisters must be left intact unless signs of infection supervene.

2. Anti-infective measures and wound care—Frostbite increases susceptibility to tetanus and infection. Tetanus prophylaxis status must be verified and updated as needed. Infection risk may be reduced by aseptic wound care. Non-adherent sterile gauze and fluffy dressing must be loosely applied to wounds and cushions used for all areas of pressure. Topical aloe vera cream or gel should be applied to the thawed tissue before application of dressings. Antibiotics should not be administered empirically.

B. Medical and Surgical Treatment Options

Telemedicine may be used so that specialists can provide advice on early field treatment of cold-injured patients in remote areas, thereby improving outcomes. Nonsteroidal anti-inflammatory drugs should be administered (in the absence of contraindications) until frostbite wounds are healed or surgical management occurs. Clinicians must watch for evidence of compartment syndrome and need for fasciotomy. Eschar formation without evidence of infection may be conservatively treated. The underlying skin may heal spontaneously with the eschar acting as a biologic dressing. Rates of amputation have been reduced with the use of intravenous infusions of synthetic prostaglandins and of tissue plasminogen activators, and with intra-arterial administration of a thrombolytic within 24 hours of exposure. The rate of tissue salvage decreases with every hour of delay from rewarming to thrombolytic therapy.

C. Follow-Up Care

Patient education must include ongoing care of the cold injury and prevention of future hypothermia and cold injury. Gentle, progressive physical therapy to promote circulation should be instituted as tolerated.

► Prognosis

Recovery from frostbite depends on the underlying comorbidities, the extent of initial tissue damage, the rewarming reperfusion injury, and the late sequelae. The involved extremity may be at increased susceptibility for discomfort and injury upon re-exposure to cold. Neuropathic sequelae include pain, numbness, tingling, hyperhidrosis, and cold sensitivity of the extremities. Nerve conduction abnormalities may persist for many years after a cold injury.

► When to Admit

- Management of tissue damage, comorbidities, associated injuries.
- Need for hospital-based interventions.
- Psychosocial factors that could compromise patient safety or recovery.

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McIntosh SE et al. Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite: 2019 update. *Wilderness Environ Med.* 2019;30:S19. [PMID: 31326282]

Shenaq DS et al. Urban frostbite: strategies for limb salvage. *J Burn Care Res.* 2019;40:613. [PMID: 30990527]

DROWNING



ESSENTIALS OF DIAGNOSIS

- The first requirement of rescue is immediate rescue breathing and CPR.
- Clinical manifestations include hypoxemia, pulmonary edema, and hypoventilation.
- Patients must be assessed for hypothermia, hypoglycemia, alcohol intake, concurrent injuries, and medical conditions.

► General Considerations

Drowning, as defined by the World Health Organization, is any “process resulting in primary respiratory impairment from submersion in a liquid medium.” Drowning may result in asphyxiation (from fluid aspiration or laryngospasm), hypoxemia, hypothermia, and acidemia. Outcomes from drowning range from life without morbidity to death. Morbidity may be immediate or delayed. A patient may be deceptively asymptomatic during the initial

recovery period only to deteriorate or die as a result of acute respiratory failure within the following 12–24 hours. Disseminated intravascular coagulation may also lead to bleeding after asphyxiation from drowning.

Drowning is a leading cause of death in children and is highly preventable in all ages with implementation of educational and safety measures. Clinicians must provide patient education and guidance about drowning prevention.

► Clinical Findings

A. Symptoms and Signs

The patient's appearance may vary from asymptomatic to marked distress with abnormal vital signs. Symptoms and signs include respiratory difficulty, chest pain, dysrhythmia, hypotension, cyanosis, and hypothermia (from cold water or prolonged submersion). A pink froth from the mouth and nose indicates pulmonary edema. The patient may experience headache, neurologic deficits, and altered level of consciousness.

B. Laboratory Findings

Metabolic acidosis is common and arterial blood gas results may be helpful in determining the degree of injury since initial clinical findings may appear benign. PaO_2 is usually decreased; Paco_2 may be increased or decreased; pH is decreased. Bedside blood sugar must be checked rapidly. Other testing is based on clinical scenario.

► Prevention

Education and prevention are critical given the high burden of disease from drowning.

Preventive measures must be taken to reduce morbidity and mortality from drowning. Conditions that increase risk of submersion injury include the use of alcohol, psychotropics, and other drugs, inadequate water safety skills, poor physical health, hyperventilation, sudden acute illness, acute trauma, decompression sickness, dangerous water conditions, and environmental hazards (eg, lack of fencing around pools).

► Treatment

A. First Aid

- The first requirement of rescue is immediate basic life support treatment and CPR.* At the scene, immediate airway management and measures to combat hypoxemia are critical to improve outcome.
- Patient must be assessed for hypothermia, hypoglycemia, concurrent medical conditions, and associated trauma.
- Rescuer must not attempt to drain water from the victim's lungs.
- Resuscitation and basic life support efforts must be continued until core body temperature reaches 32°C.

B. Subsequent Management

- 1. Ensure optimal ventilation and oxygenation**—The onset of hypoxemia exists even in the alert, conscious

patient who appears to be breathing normally. Oxygen must be administered immediately at the highest available concentration. Oxygen saturation must be maintained at 90% or higher via some form of supplemental oxygen.

Serial physical examinations and chest radiographs must be performed to detect possible pneumonitis, atelectasis, and pulmonary edema. Bronchodilators may be used to treat wheezing. Nasogastric suctioning may be necessary to decompress the stomach.

- 2. Cardiovascular support**—Intravascular volume status must be monitored and supported by vascular fluid replacement, vasopressors, or diuretics as needed.

- 3. Correction of blood pH and electrolyte abnormalities**—Metabolic acidosis is present in the majority of drowning victims, but this typically corrects through adequate ventilation and oxygenation. Glycemic control improves outcome.

- 4. Cerebral and spinal cord injury**—Central nervous system damage may progress despite apparently adequate treatment of hypoxia and shock.

- 5. Hypothermia**—Core body temperature must be measured and managed as appropriate (see Accidental Systemic Hypothermia, above).

► Course & Prognosis

As the duration of submersion lengthens, the probability of worse outcomes increases. Favorable prognosis is related to a duration of submersion less than 5 minutes. Respiratory damage is often severe in the minutes to hours following a drowning. With appropriate respiratory supportive treatment, patients may improve rapidly over the first few days following the drowning. Long-term complications of drowning may include neurologic impairment, seizure disorder, and pulmonary or cardiac damage. Prognosis is directly correlated with the patient's age, submersion time, rapidity of prehospital resuscitation and subsequent transport to a medical facility, clinical status at time of arrival to hospital, Glasgow Coma Scale score, pupillary reactivity, and overall health assessment (APACHE II score).

► When to Admit

Most patients with significant drowning or concurrent medical or traumatic conditions require inpatient monitoring following the event. This includes continuous monitoring of cardiorespiratory, neurologic, renal, and metabolic function. Pulmonary edema may not appear for 24 hours.

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THERMAL BURNS



ESSENTIALS OF DIAGNOSIS

- ▶ Estimates of the burn location, size, and depth greatly determine the treatment plan.
- ▶ The first 48 hours of burn care offer the greatest impact on morbidity and mortality of a burn victim.

Worldwide, burns are a common cause of injury and potential morbidity and mortality. Burn prognosis is affected by the type of environment where the burn occurred. Low-resource settings (wilderness or low-income areas) are associated with delays in and suboptimal access to standard burn treatments.

The first 48 hours after thermal burn injury offer the greatest opportunity to impact the survival of the patient. Early surgical intervention, wound care, enteral feeding, glucose control and metabolic management, infection control, and prevention of hypothermia and compartment syndrome have contributed to significantly lower mortality rates and shorter hospitalizations. Research utilizing several different well-established burn severity scores has shown the importance of patient comorbidities to the prognosis of patients with severe burn injuries.

► General Considerations

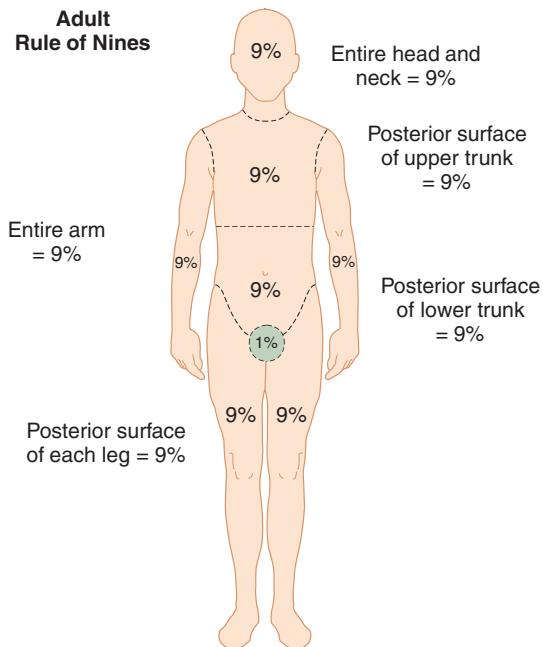
A. Classification

Burns are classified by extent, depth, patient age, and associated illness or injury. Accurate estimation of burn size and depth is necessary to quantify the parameters of resuscitation.

1. Extent—In adults, the “rule of nines” (Figure 37–2) is useful for rapidly assessing the extent of a burn. It is important to view the entire patient to make an accurate assessment of skin findings on initial and subsequent examinations. One rule of thumb is that the palm of an open hand in adult patients constitutes 1% of total body surface area (TBSA). TBSA is calculated for partial- and full-thickness burns.

2. Depth—Judgment of depth of injury is difficult. **Superficial burns** may appear red or gray but will demonstrate excellent capillary refill and are not blistered initially. If the wound is blistered and appears pink and wet, this represents a **superficial partial-thickness burn**. **Deep partial-thickness burns** appear white and wet, and bleed if poked; cutaneous sensation is maintained. **Full-thickness burns** result in a loss of adnexal structures and may appear white-yellow in color, or may have a black charred appearance. This stiff, dry skin does not bleed when poked and cutaneous sensation is lost.

Deep partial-thickness and full-thickness burns are treated in a similar fashion. Both require early debridement and grafting to heal appropriately, without which the skin becomes thin and scarred.



▲ Figure 37–2. Estimation of body surface area in burns.

B. Survival After Burn Injury

Transfer to a burn unit is determined by large burn size, circumferential burn, or burn involving a joint or high-risk body part, and by comorbidities. Mortality rates have been significantly reduced due to treatment advances including improvements in wound care, treatment of infection, early burn excision, skin substitute usage, and early nutritional support.

C. Associated Injuries or Illnesses

Smoke inhalation, associated trauma, and electrical injuries are commonly associated with burns. Severe burns from any source may result in similar complications (eg, infections, respiratory compromise, multiorgan dysfunction, venous thromboembolism, and gastrointestinal complications).

D. Systemic Reactions to Burn Injury

Burns greater than approximately 20% of TBSA may lead to systemic metabolic derangements requiring intensive support. The inflammatory cascade can result in shock and coagulopathy.

► Treatment

A. Initial Resuscitation

1. Primary survey—Burn patients require a full trauma assessment, starting with “ABCDE” (airway, breathing, circulation, disability, exposure).

A. AIRWAY CONTROL—Serial assessments of airway and breathing are necessary because airway compromise and

ARDS may develop, particularly in those with inhalation injury.

B. VASCULAR ACCESS—Vascular access must be obtained on all burn patients.

C. FLUID RESUSCITATION—Patients with burns greater than 15% of TBSA require intravascular fluid administration of large volumes of crystalloid. The most widely recognized guideline for fluid resuscitation is the **Parkland formula** (<https://www.mdcalc.com/parkland-formula-burns>) in which the fluid requirement in the first 24 hours is estimated as $4 \text{ mL/kg} \times \text{body weight per percent of body surface area burned}$. Half the calculated fluid is given in the first 8-hour period from the time of injury, not the time of arrival to medical care. The remaining fluid is delivered over the next 16 hours. An extremely large volume of fluid may be required. Crystalloid solutions alone may be insufficient to restore cardiac preload during the period of burn shock. Conversely, clinicians must watch for clinical signs of volume overload as it may lead to pulmonary complications or to a compartment syndrome from edema. Electrical burns and inhalation injury may increase the fluid requirement.

B. Management

1. Pain control—Pain control is critical in burn injury patients. Treatment is with (oral or intravenous) nonsteroidal anti-inflammatory drugs and opioids (see Chapter 5).

2. Chemoprophylaxis—

A. TETANUS IMMUNIZATION—Verify and update tetanus prophylaxis status in all burn patients. (See Chapter 33.)

B. ANTIBIOTICS—All nonsuperficial wounds need to be covered with topical antibiotics. Prophylaxis with systemic antibiotics is not indicated.

3. Surgical management—

A. ESCHAROTOMY—As tissue swelling occurs, ischemia may develop under any constricting eschar of an extremity, neck, or chest, or in circumferential full-thickness burns of the trunk. Escharotomy incisions can be life- and limb-saving.

B. FASCIOTOMY—Fasciotomy is indicated for any compartment syndrome. Clinicians must frequently monitor patients for development of early signs of a compartment syndrome, particularly in those with circumferential burns.

C. DEBRIDEMENT, DRESSINGS, AND TOPICAL AND SYSTEMIC ANTIBIOTIC THERAPY—Minor burn wounds must be debrided to determine the depth of the burn and then thoroughly cleansed. Thereafter, daily wound care must consist of debridements as needed, topical antibiotics, and wound dressings. Patient compliance and adequate pain control is essential for successful outpatient treatment. The wound must be reevaluated by the treating clinician within 24–72 hours to evaluate for signs of infection.

The goal of burn wound management is to protect the wound from desiccation and avoid further injury or infection. Regular and thorough cleansing of burned areas is of

critical importance. Topical antibiotics may be applied after wound cleansing. Silver sulfadiazine is no longer recommended.

It is imperative to closely monitor for and treat systemic infection, since this remains a leading cause of morbidity among patients with major burn injuries. Health care-associated infections are increasingly common.

D. WOUND MANAGEMENT—The goal of therapy after fluid resuscitation is rapid and stable closure of the wound. Wounds that do not heal spontaneously in 7–10 days (eg, deep partial-thickness or full-thickness burns) are best treated by a specialist through excision and autograft to avoid development of granulation and infection. The quality of the skin in regenerated deep partial-thickness burns is marginal because of the very thin dermis that emerges.

Cultured allogeneic keratinocyte grafts can provide rapid early coverage for superficial burn injuries. Skin substitution with cultured grafts may be life-saving for severe burns. Although the replaced dermis has nearly normal histologic dermal elements, there are no adnexal structures present, and very few, if any, elastic fibers.

E. ABDOMINAL COMPARTMENT SYNDROME—Abdominal compartment syndrome is a potentially lethal condition that may develop in severely burned patients, with mortality rates of approximately 60% despite surgical intervention. Diagnosis is confirmed by bladder pressures greater than 30 mm Hg in at-risk patients. Surgical abdominal decompression may improve ventilation and oxygen delivery but may not impact survival.

C. Patient Support

Burn patients require extensive supportive care, both physiologically and psychologically. It is important to maintain normal core body temperature and avoid hypothermia, by maintaining environmental temperature at or above 30°C, in patients with burns over more than 20% of TBSA. Burn patients are at risk for many complications such as respiratory injury, ARDS or respiratory failure unresponsive to maximal ventilatory support, sepsis, multiorgan failure, and venous thromboembolism.

Burn patients have increased metabolic and energy needs for wound healing and require careful assessment and provision of optimal nutrition. Early aggressive nutrition (by parenteral or enteral routes) reduces infections, recovery time, noninfectious complications, length of hospital stay, long-term sequelae, and mortality.

Prevention of long-term scars remains a formidable problem in seriously burned patients.

► Prognosis

Prognosis depends on the extent and location of the burn tissue damage, associated injuries, comorbidities, and complications. Hyperglycemia is a predictor of worse outcomes. Common complications include sepsis; gangrene requiring limb amputation; or neurologic, cardiac, cognitive, or psychiatric dysfunction. Psychiatric support may be necessary following burn injury.

► When to Refer

Transfer to a burn unit is indicated for large burn size (for partial-thickness burns greater than 10% of TBSA or for full-thickness burns greater than 5% of TBSA), circumferential burn, inhalation injury, or burn involving a joint or high-risk body part (face, hands, feet, genitalia), and for patients with comorbidities.

► When to Admit

- All severe burn patients require extensive supportive care, both physiologically and psychologically.
- Significant burns (based on location and extent).
- Patients with significant comorbidities and suboptimal home situations.
- Burn center consultation can advise which patients require transfer and which can be managed via telemedicine/telephone consultation.
- Monitoring includes vital signs, wound care, and observation for potential complications of electrolyte abnormalities, acute kidney injury, hepatic failure, cardiopulmonary compromise, hyperglycemia, and infection.

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Otterness K et al. Emergency department management of smoke inhalation injury in adults. *Emerg Med Pract.* 2018;20:1. [PMID: 29489306]

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ELECTRICAL INJURY



ESSENTIALS OF DIAGNOSIS

- ▶ Extent of injury is determined by the type, amount, duration, and pathway of electrical current.
- ▶ Clinical findings of death are unreliable; therefore, resuscitation efforts must be attempted before assuming the electrical injury victim is dead.
- ▶ Skin findings may be misleading and are not indicative of the depth of tissue injury.

► General Considerations

Electricity-induced injuries are common and yet most are preventable. These injuries occur by exposure to electrical current of low voltage, high voltage, or lightning. Electrical current type is either alternating current (AC) or direct current (DC) and is measured in volts (V). Electricity causes acute injury by direct tissue damage, muscle tetany, direct thermal injury and coagulation necrosis, and associated trauma.

Alternating current (AC) is an electric current that periodically reverses direction in a sine wave pattern and may cause muscle tetany, which prolongs the duration and

amount of current exposure. AC can be low voltage or high voltage. Most households and businesses use electric power in the form of AC at **low voltages** (less than 1000 V). Low voltage electrical injuries can range from minor to significant damage and death. **High voltage** (greater than 1000 V) AC electrical injuries are often related to occupational exposure and associated with deep tissue damage and higher morbidity and mortality. **Direct current (DC)** is unidirectional electrical flow (eg, lightning, batteries, and automotive electrical systems). It is more likely to cause a single intense muscle contraction and asystole. **Lightning** differs from other high-voltage electrical shock because lightning delivers a direct current of millions of volts in a fraction of a second.

The extent of damage from electrical injuries depends on the following factors: voltage, current type, tissue resistance, moisture, pathway, duration of exposure, associated trauma, and comorbidities. Current is the most important determinant of tissue damage. Current passes through the tissues of least resistance as energy, which produces heat and causes direct thermal injury. Tissue resistance varies throughout the body with nerve cells being the most vulnerable and bone the most resistant to electrical current.

► Clinical Findings

Electrical burns are of three distinct types: flash (arcing) burns, flame (clothing) burns, and the direct heating effect of tissues by the electrical current.

Skin damage does not correlate with the degree of injury. Not all electrical injuries cause skin damage; very minor skin damage may be present with massive internal injuries. Symptoms and signs may range from very subtle to death. The presence of entrance and exit burns signifies an increased risk of deep tissue damage. Current passing through skeletal muscle can cause muscle necrosis and contractions severe enough to result in bone fracture. If the current passes through the heart or brainstem, death may be immediate due to ventricular fibrillation, asystole, or apnea.

Resuscitation must be initiated on all victims of electrical injury since clinical findings are deceptive and unreliable.

► Complications

Complications include cardiac or respiratory arrest; dysrhythmias; neurologic dysfunction (eg, autonomic dysfunction; altered mental status; seizures); paralysis; headache; neuropathy; vascular injury; tissue edema and necrosis; compartment syndrome; associated traumatic injuries; pneumothorax; rhabdomyolysis; acute kidney injury; hypovolemia; infections; ocular complications; sepsis; gangrene; and cognitive or psychiatric dysfunction. Psychiatric support may be necessary following electrical injury.

► Treatment

A. Emergency Measures

The patient must be assessed and treated as a trauma victim. The patient must be safely separated from the electrical current prior to initiation of CPR or other treatments. *Resuscitation must be initiated since clinical findings of death are unreliable.*

B. Hospital Measures

The initial assessment involves airway, breathing, and circulation followed by a full trauma protocol. Fluid resuscitation is important to maintain adequate urinary output. Initial evaluation includes cardiac monitoring and ECG, complete blood count, electrolytes, kidney function tests, liver chemistries, creatine phosphokinase or urine myoglobin, urinalysis, and cardiac enzymes. ECG does not show typical patterns of ischemia since the electrical damage is epicardial. Victims must be evaluated for hidden injury, organ injury, blunt trauma, dehydration, skin burns, hypertension, acid-base disturbances, and neurological as well as psychological damage.

Electrical burn wounds are an underrecognized, yet devastating form of burn injury with wide-ranging and significant complications.

When electrical injury occurs, there must be a high suspicion for extensive deep tissue necrosis. Superficial skin may appear deceptively benign. Deep tissue necrosis leads to profound tissue swelling, resulting in a high risk of a compartment syndrome. Early debridement of devitalized tissues and tetanus prophylaxis may reduce the risks of infection.

Pain management is important before, during, and after initial treatment and subsequent rehabilitation.

► Prognosis

Prognosis depends on the degree and location of electrical injury, initial tissue damage, associated injuries, comorbidities, and complications.

► When to Refer

- Specialists may need to perform fasciotomy for compartment syndrome, debridement of devitalized tissue, or microvascular reconstruction.
- Ophthalmologists should evaluate patients for possible ocular complications; ENT physicians should evaluate for tympanic membrane rupture or hearing loss.

► When to Admit

Indications for hospitalization include high-voltage exposure; dysrhythmia or ECG changes; large burn size; neurologic, pulmonary, or cardiac symptoms; suspicion of significant deep tissue or organ damage; transthoracic current pathway; history of cardiac disease or other significant comorbidities or injuries; and need for surgery.

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Waldmann V et al. Electrical cardiac injuries: current concepts and management. *Eur Heart J*. 2018;39:1459. [PMID: 28444167]

RADIATION EXPOSURE



ESSENTIALS OF DIAGNOSIS

- Damage from radiation is determined by the source, type, quantity, duration, bodily location, and susceptibility and accumulation of exposures of the person.
- Clinicians and patients must be educated regarding the risks of medical diagnostic radiation weighed against the benefits of the medical imaging needed.

► General Considerations

Radiation exposure may occur from environmental, occupational, medical care, accidental, or intentional causes. The extent of damage from radiation exposure depends on the type, quantity, and duration of radiation exposure; the organs exposed; the degree of disruption to DNA; metabolic and cellular function; and the age, underlying condition, susceptibility, comorbidities, and accumulative exposures of the victim.

Radiation occurs from both nonionizing and ionizing radiation sources. **Nonionizing radiation** is low energy, resulting in injuries related to local thermal damage (eg, microwave, ultraviolet, visible light, and radiowave). **Ionizing radiation** is high energy, causing bodily damage in several ways. Exposure may be external, internal, or both. Radiation exposure triggers multiple metabolic changes on the molecular and cellular levels resulting in tissue-specific damage.

The International Commission on Radiological Protection (ICRP) website provides the most up-to-date recommendations for protection against ionizing radiation (<http://www.icrp.org/index.asp>). The World Health Organization (WHO) publishes guidelines on radiation emergencies (https://www.who.int/ionizing_radiation/a_e/en/). These guidelines include recommended interventions during the early, intermediate, and late emergency phases and the management of their psychosocial impact.

► Clinical Findings

Radiation exposure results in acute and delayed effects. It is important to obtain the event history in order to assess the amount of radiation exposure, and the possibility of coexisting injuries or conditions. Acute effects involve damage of the rapidly dividing cells (eg, the mucosa, skin, and bone marrow). This may be manifested as mucositis, nausea, vomiting, gastrointestinal edema and ulcers, skin burns, and bone marrow suppression over hours to days after exposure. Delayed effects include malignancy, reproduction abnormalities, and liver, kidney, and central nervous system and immune system dysfunction.

Acute radiation syndrome is due to an exposure to high doses of ionizing radiation over a brief time course.

Clinicians must be educated to recognize and treat acute radiation sickness. The symptom onset is within hours to days depending on the dose. Symptoms include anorexia, nausea, vomiting, weakness, exhaustion, lassitude and, in some cases, prostration; these symptoms may occur singly or in combination. Dehydration, anemia, and infection may follow. The Centers for Disease Control and Prevention offers information regarding acute radiation syndrome (<https://www.cdc.gov/nceh/radiation/emergencies/arsphysicianfactsheet.htm>).

In acute radiation exposure, medical care includes close monitoring of the gastrointestinal, cutaneous, hematologic, cardiopulmonary, and cerebrovascular symptoms and signs from initial exposure and over time.

► Therapeutic Radiation Exposure

Radiation therapy has been a successful component in the treatment of many malignancies. These radiation-treated cancer survivors have a higher risk of development of a second malignancy; obesity; and pulmonary, cardiac, and thyroid dysfunction, as well as an increased overall risk for chronic health conditions and mortality.

► Medical Imaging Radiation Exposure

Medical imaging with ionizing radiation exposure has dramatically increased over the past few decades. With the rising use of medical imaging, there is international focus on improving the safety by standardization and regulation of radiation dosing in medical diagnostics and education for clinician and the public about this issue.

The American College of Radiology (ACR) provides “ACR Appropriateness Criteria,” which are evidence-based guidelines created by expert panels to serve as a reference for best practices for imaging decisions by health care providers (<https://www.acr.org/Clinical-Resources/ACR-Appropriateness-Criteria>). Clinicians and patients must carefully weigh the risks and benefits of radiation exposure when deciding on an imaging test.

► Occupational & Environmental Radiation Exposure

Useful resources for professionals include both the Centers for Disease Control and Prevention “Radiation Emergencies” website (<https://www.cdc.gov/nceh/radiation/emergencies/index.htm>) and the National Nuclear Security Administration’s Radiation Emergency Assistance Center which provides 24-hour access to expert consultation services (telephone: 1-865-576-1005 or website: <https://orise.orau.gov/reacts/>).

► Treatment

Treatment is focused on decontamination, symptomatic relief, supportive care, and psychosocial support and management of coexisting conditions or injuries. Specific supportive treatments are determined by the dose, route, and effects of exposure and associated conditions present.

► Prognosis

Prognosis is determined by the radiation dose, duration, and frequency as well as by the underlying condition of the victim. Death is usually due to hematopoietic failure, gastrointestinal mucosal damage, central nervous system damage, widespread vascular injury, or secondary infection.

Carcinogenesis is related to the radiation type, total dose, duration, and accumulation of exposure, and to the susceptibility of the victim. Radiation-related cancer risks persist throughout the exposed person's life span.

With the increased use of ionizing radiation for medical diagnostics and treatments, there is a growing concern for the iatrogenic increase in radiation-induced cancer risks. There are age-related sensitivities to radiation; prenatal and younger age victims are more susceptible to carcinogenesis.

► When to Admit

Most patients with significant ionizing radiation exposure require admission for close monitoring and supportive treatment.

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ENVIRONMENTAL DISORDERS RELATED TO ALTITUDE

DYSBARISM & DECOMPRESSION SICKNESS

ESSENTIALS OF DIAGNOSIS

- Symptoms temporally related to recent altitude or pressure changes.
- Early recognition and prompt treatment of decompression illness are extremely important.
- Patient must also be assessed for hypothermia, hypoglycemia, concurrent injuries, and medical conditions.
- Consultation with diving medicine or hyperbaric oxygen specialist is indicated.

► General Considerations

Dysbarism and decompression illness are physiologic problems that result from altitude changes and the effects

of environmental pressure on the gases in the body during underwater descent and ascent. These are most likely to occur when scuba diving is followed closely by travel to high altitudes, or when the scuba diver is not adherent to the conservative dive guidelines for dive duration, course, depth, and surface times.

As a diver begins to descend, the gases in the body compress and dissolve in the blood and the tissues. These gases dissolve throughout areas of the body that are both compressible (lungs, gastrointestinal tract) and noncompressible (sinuses, joints). When the diver descends further, there is increased pressure on the gases to dissolve even more into the bloodstream and these tissues. During the subsequent ascent, the dissolved gases expand. The gas compression and expansion depend on the difference between the atmospheric pressure and the partial pressure of the gas dissolved in the tissues.

Dysbarism results from barotrauma when gas compression or expansion occurs in parts of the body that are non-compressible or have limited compliance. Pulmonary overinflation syndrome is one of the most serious and potentially fatal results of barotrauma. This syndrome is due to an inappropriately rapid ascent causing alveoli rupture and air bubble extravasation into tissue planes or even the cerebral circulation.

Decompression illness occurs when the pressure change is too rapid from higher pressure to lower pressure. The result is that gas bubbles form and cause damage depending on their location (eg, coronary, pulmonary, spinal or cerebral blood vessels, joints, soft tissues). Decompression illness symptoms depend on the size, number, and location of released gas bubbles (notably nitrogen). Risk of decompression illness in scuba diving depends on multiple factors: the dive details (depth, duration, number of dives, interval surface time between dives, and water conditions). Patient factors include age, weight, overall health, physical condition, physical exertion, the rate of ascent, and the length of time between the low altitude (scuba dive) and high altitude (ground ascent or air travel). Predisposing factors include obesity, injury, hypoxia, lung or cardiac disease, right to left cardiac shunt, dehydration, alcohol and medication effects, and panic attacks. Decompression illness may also occur in those who take hot showers after cold dives.

Preventive measures include pre-dive medical screening and dive planning; diver education; strict adherence to dive course, timing, and depths; and a slow and controlled ascent plus proper control of buoyancy. Conservative recommendation is to avoid high altitudes (ground ascent or air travel) for at least 24 hours after surfacing from the dive, especially following multiple dives.

Clinical Findings

There is a range of clinical manifestations depending on the location of the gas bubble formation or the compressibility of gases in the body. Symptom onset may be immediate or within minutes or hours (in the majority), up to 48 hours later. Decompression illness symptoms include pain in the joints ("the bends"); skin pruritus or burning ("skin bends"); cardiac symptoms (acute coronary syndrome, conduction abnormalities); spinal cord or cerebral

symptoms (focal neurologic dysfunction or "dissociation" symptoms that do not follow typical distribution neuro-anatomic patterns); labyrinthine decompression illness ("the staggers," central vertigo); pulmonary decompression illness ("the chokes," inspiratory pain, cough, and respiratory distress); arterial gas embolism (cerebral, pulmonary); barotrauma of the lungs, ear, and sinus; and coma and death.

Decompression illness involving the brain and spinal cord may occur by different mechanisms due to air bubbles causing arterial occlusion, venous obstruction, or *in situ* toxicity.

The clinician must assess for associated conditions of hypothermia, hypoglycemia, hypovolemia, drowning, trauma, envenomation, or concurrent medical conditions.

Treatment

Early recognition and prompt treatment are extremely important. Decompression illness must be considered if symptoms are temporally related to recent diving or rapid changes in altitude or pressure within the past 48 hours. Continuous administration of 100% oxygen is indicated and beneficial for all patients. Hyperbaric oxygen treatment is commonly recommended for decompression illness symptoms. Immediate consultation with a diving medicine or hyperbaric oxygen specialist is indicated even if mild decompression illness symptoms resolve. Nonsteroidal anti-inflammatory drugs, acetaminophen, or aspirin may be given for pain control if there are no contraindications. *Opioids must be used very cautiously*, since these may obscure the response to recompression.

When to Admit

Rapid transportation to a hyperbaric treatment facility for recompression is imperative for decompression illness. The Divers Alert Network is an excellent worldwide resource for emergency advice 24 hours daily for the management of diving-related conditions (www.dan.org).

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HIGH-ALTITUDE ILLNESS



ESSENTIALS OF DIAGNOSIS

- The severity of the high-altitude illness is affected by the rate and height of ascent and the individual's susceptibility.
- Prompt recognition and medical treatment of early symptoms of high-altitude illness may prevent progression.

- ▶ Clinicians must assess other conditions that may coexist or mimic symptoms of high-altitude illness.
- ▶ Immediate descent is the definitive treatment for high-altitude cerebral edema and high-altitude pulmonary edema.

► General Considerations

As altitude increases, there is a decrease in both barometric pressure and oxygen partial pressure resulting in hypobaric hypoxia. High-altitude illnesses are due to hypobaric hypoxia at high altitudes (usually greater than 2000 meters or 6562 feet). High-altitude illness includes a spectrum of disorders categorized by end-organ effects (mostly cerebral and pulmonary) and exposure duration (acute and long-term). Acute high-altitude illnesses are **acute hypoxia**, **acute mountain sickness (AMS)**, **high-altitude cerebral edema (HACE)**, and **high-altitude pulmonary edema (HAPE)**.

Acclimatization occurs as a physiologic response to the increasing altitude and increasing hypobaric hypoxia. High-altitude illness results when the hypoxic stress is greater than the individual's ability to acclimatize. Risk factors for high-altitude illness include increased physical activity with insufficient acclimatization, inadequate education and preparation, individual susceptibility, and previous high-altitude illness. The key determinants of high-altitude illness risk and severity include both individual susceptibility factors and altitudinal factors, such as rate and height of ascent and total change in altitude over time.

Individual susceptibility factors include underlying conditions such as cardiac and pulmonary disease, patent foramen ovale, blood disorders, pregnancy, neurologic conditions, smoking, recent surgery, diabetes mellitus, and many other chronic medical conditions. Those with symptomatic neurologic, cardiac, or pulmonary disease must avoid high altitudes.

Patient assessment for high-altitude illness must also include evaluation for other conditions, which may coexist or may present in a similar manner.

1. High-Altitude–Associated Neurologic Conditions: AMS & HACE

There is a spectrum of neurologic conditions caused by high altitude, ranging from **acute mountain sickness (AMS)** to the more serious form, **high-altitude cerebral edema (HACE)**

AMS includes symptoms such as headache (most severe and persistent symptom), lassitude, drowsiness, dizziness, chilliness, nausea and vomiting, and difficulty sleeping. Later symptoms include irritability, difficulty concentrating, anorexia, insomnia, and increased headaches.

HACE includes the severe symptoms of AMS and results from cerebral vasogenic edema and cerebral cellular hypoxia. It usually occurs at elevations above 2500 meters (8202 feet) but may occur at lower elevations. Hallmarks are altered mental status, ataxia, severe lassitude, and encephalopathy. Examination findings may include

confusion, ataxia, urinary retention or incontinence, focal neurologic deficits, papilledema, and seizures. Symptoms may progress to obtundation, coma, and death.

► Treatment

Definitive treatment is immediate descent of at least 610 meters (2001 feet), and descent must continue until symptoms improve. Descent is essential if the symptoms are persistent, severe, or worsening, or if HACE or HAPE is present. If immediate descent is not possible, portable hyperbaric chambers can provide symptomatic relief, but this must not delay descent.

Initial treatment involves oxygen administration to keep the pulse oximetry S_pO_2 to greater than 90%.

Acetazolamide is an effective medication for both prophylaxis and treatment of mild symptoms of AMS.

Dexamethasone is given for moderate to severe AMS. Dexamethasone is the primary treatment for HACE. Acetazolamide can be added as an adjunct in severe HACE cases. In most individuals, symptoms clear within 24–48 hours. HACE treatment must continue until 24 hours after resolution of symptoms or until descent is completed. Dexamethasone should not be given for longer than 7 days.

It is imperative that the clinician also assess for other conditions that may mimic or coexist with AMS and HACE.

If HAPE symptoms and signs are present along with HACE, nifedipine or a selective phosphodiesterase inhibitor may be added for pulmonary vasodilation. The clinician must be cautious when using combinations of vasodilators.

2. Acute HAPE

HAPE is the leading cause of death from high-altitude illness. The hallmark is markedly elevated pulmonary artery pressure followed by pulmonary edema. Early symptoms may appear within 6–36 hours after arrival at a high-altitude area. These include incessant dry cough, shortness of breath disproportionate to exertion, headache, decreased exercise performance, fatigue, dyspnea at rest, and chest tightness. Recognition of the early symptoms may enable the patient to descend before incapacitating pulmonary edema develops. Strenuous exertion must be avoided. As pulmonary edema worsens, wheezing, orthopnea, and hemoptysis may develop.

Physical findings may include tachycardia, mild fever, tachypnea, cyanosis, prolonged respiration, rales, wheezing, and rhonchi. The clinician must assess for other potential medical conditions because the clinical picture may resemble other entities. Diagnosis is usually clinical; ancillary tests are nonspecific or unavailable on site. Prompt recognition and medical attention of early symptoms of HAPE may prevent progression.

► Treatment

Immediate descent (at least 610 meters [2000 feet]) is essential, although this may not be immediately possible and may not alone improve symptoms.

The patient must be placed at rest, reclined with head elevated. Supplemental oxygen must be administered to maintain pulse oximetry readings of S_pO_2 greater than 90%. Recompression in a portable hyperbaric bag will temporarily reduce symptoms if rapid or immediate descent is not possible, but must not delay descent.

Nifedipine can be used as an adjunct if the other therapies (descent, oxygen, or portable hyperbaric chambers) are not successful or available. Selective phosphodiesterase inhibitors may be used for HAPE prevention and may also provide effective symptom relief as an alternative or if nifedipine is not available. *Administering nifedipine plus a phosphodiesterase inhibitor as pulmonary vasodilators is not recommended* because this combination may also lower the mean arterial pressure and decrease cerebral perfusion. Treatment for ARDS (see Chapter 9) is required for some patients. If neurologic symptoms are present concurrently with HAPE and do not resolve with improved oxygenation, dexamethasone may be added according to HACE treatment guidelines.

There is an international effort to advance the understanding of high-altitude pulmonary edema through the research and database registry (<https://www.altitude.org>).

► Prevention of High-Altitude Disorders

Pre-trip preventive measures include participant education, medical preparticipation evaluation, pre-trip planning, optimal physical conditioning before travel, and adequate rest and sleep the day before travel and during the trip. Preventive efforts during ascent include reduced food intake, avoidance of alcohol and tobacco, and limiting any unnecessary physical activity during travel.

Gradual ascent is the most effective way to allow acclimatization. Low-risk ascension rate is 2 or more days to arrive at 2500–3000 meters. The altitude reached during waking hours is not as important as the altitude at which the hiker sleeps. Mountaineering parties at altitudes of 3000 meters or higher must carry a supply of oxygen and medical equipment sufficient for several days.

Drug prophylaxis may be prescribed for AMS and HACE if no contraindications exist. Prophylactic low-dose acetazolamide has been shown to reduce the incidence and severity of AMS and HACE when started 3 days prior to ascent and continued for 48–72 hours at high altitude. Dexamethasone is an alternative prophylactic medication for AMS and HACE.

Individuals with a past history of HAPE should use drug prophylaxis to reduce the risk of recurrence. Nifedipine started the day before ascent and continued through the fourth day at target elevation, or through the seventh day if the ascent rate was faster, is recommended. Salmeterol can be added beginning 24 hours prior to ascent. Salmeterol is used as an adjunct to nifedipine but not as monotherapy.

Phosphodiesterase inhibitors may be beneficial in the treatment of HAPE based on their physiologic effects of decreased pulmonary arterial pressures and pulmonary vasodilation.

► When to Admit

- All patients with HACE or HAPE must be hospitalized for further observation.
- Hospitalization must also be considered for any patient who remains symptomatic after treatment and descent.
- Pulmonary symptoms and hypoxia may be worsened by complications such as pulmonary embolism, secondary respiratory infection, bronchospasm, mucous plugging, or acute coronary syndrome.

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SAFETY OF AIR TRAVEL & SELECTION OF PATIENTS FOR AIR TRAVEL

The medical safety of air travel depends on the nature and severity of the traveler's preflight condition and factors such as travel duration and frequency of travel, use and frequency of inflight exercise, cabin altitude pressure, availability of medical supplies, infectious diseases of other travelers, and the presence of health care professionals on board. Air travel passengers are susceptible to a wide range of flight-related problems: pulmonary (hypoxemia, spontaneous pneumothorax), venous thromboembolism (VTE), infections, cardiac, gastrointestinal, ocular, immunologic, syncope, neuropsychiatric, metabolic, trauma, and illicit substance-related conditions. Air travel risks are higher for those air travelers with preexisting medical conditions.

Hypobaric hypoxia is the underlying etiology of most serious medical emergencies in flight due to cabin altitude. Despite commercial aircraft pressurization requirements, there is significant hypoxemia, dyspnea, gas expansion, and stress in travelers, particularly in those with underlying pulmonary disease.

Air travel has been the main focus of medical reviews on travel-related VTE; however, any form of prolonged travel involving immobilization is associated with increased risk of VTE (now referred to as "traveler's thrombosis"). VTE risk is more relevant for those passengers with additional VTE risk factors. Risks for VTE in long-distance travelers include the following: (1) travel involving immobilization for 4 or more hours, (2) hypercoagulable disorders, and (3) acquired risks. Prevention measures may include wearing graduated compression stockings; frequent exercise and position changes during travel; and the use of thromboprophylaxis, such as low-molecular-weight heparin (LMWH) or direct-acting oral anticoagulant (DOAC) (see Chapter 14).

Air travel is not advised for anyone who is "incapacitated" or has any "unstable conditions." The Air Transport Association of America defines an **incapacitated passenger** as "one who is suffering from a physical or mental disability and who, because of such disability or the effect of

the flight on the disability, is incapable of self-care; would endanger the health or safety of such person or other passengers or airline employees; or would cause discomfort or annoyance of other passengers.” **Unstable conditions** include active pneumothorax, advanced pulmonary hypertension, acute worsening of an underlying lung disease, poorly controlled hypertension, dysrhythmias, angina pectoris, valvular disease, heart failure, or acute psychiatric condition; severe anemia or symptomatic sickle cell disease; recent myocardial infarction; cerebrovascular accident; poorly controlled seizure disorder; deep venous thrombosis; postsurgery, especially heart surgery (unless approved by surgeon); and any active communicable disease. Public Health Travel Restrictions have shown efficacy in preventing commercial air or international travel of persons with certain communicable diseases that pose public health threat.

► Pregnancy

Pregnant travelers have unique travel-related and location-specific risks. A clinician’s authorization is required if travel is essential during the ninth month of pregnancy or earlier in a complicated or high-risk pregnancy.

Long travel increases risk of VTE for the pregnant traveler. Pregnant travelers are at higher risk from infection transmission and air travel radiation exposure.

► Prevention

Air travel complications may be reduced by the following preventive measures: passenger prescreening, passenger education, and in-flight positioning and activity. Prescreening evaluation is recommended for all high-risk patients including preexisting requirement for oxygen, continuous positive airway pressure or ventilator support,

underlying restrictive or obstructive lung disease, comorbidities worsened by hypoxemia, previous respiratory distress during air travel, recent pneumothorax, and recent (within 6 weeks) acute respiratory illness. Patients at risk for hypoxia must be assessed prior to air travel to determine if there is a need for supplemental in-flight oxygen.

Air travel education must include risk reduction measures for VTE, infectious diseases, and exacerbations of underlying medical conditions. Patients and clinicians can check the World Health Organization website for the most updated information on travel health risks and infectious diseases (<https://www.who.int/travel-advice>). Air travel has been associated with an increased risk of transmission of infectious diseases.

All long-distance travelers can reduce VTE risk by avoiding constrictive clothing, staying well-hydrated, changing position frequently, avoiding cramped position, avoiding leg crossing, engaging in frequent (at least every hour) in-flight leg stretching exercises, and walking for 5 minutes every hour. Clinicians must assess those with high risk of VTE prior to air travel to determine whether anticoagulation is indicated (see Table 14–14).

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Poisoning

Craig Smollin, MD

INITIAL EVALUATION: POISONING OR OVERDOSE

Patients with drug overdoses or poisoning may initially have no symptoms or they may have varying degrees of overt intoxication. The asymptomatic patient may have been exposed to or may have ingested a lethal dose, but not yet exhibit any manifestations of toxicity. It is important to (1) quickly assess the potential danger, (2) consider gut and skin decontamination to prevent absorption, (3) treat complications if they occur, and (4) observe the asymptomatic patient for an appropriate interval.

► Assess the Danger

If the drug or poison is known, its danger can be assessed by consulting a text or computerized information resource or by calling a regional poison control center. (In the United States, dialing 1-800-222-1222 will direct the call to the regional poison control center.) Assessment will usually take into account the dose ingested; the time since ingestion; the presence of any symptoms or clinical signs; preexisting cardiac, respiratory, kidney, or liver disease; and, occasionally, specific serum drug or toxin levels. Be aware that the history given by the patient or family may be incomplete or unreliable.

IMMEDIATE 24-HOUR TOXICOLOGY CONSULTATION

Call your regional poison control center
U.S. toll-free 1-800-222-1222

► Observe the Patient

Asymptomatic or mildly symptomatic patients should be observed for at least 4–6 hours. Longer observation is indicated if the ingested substance is a sustained-release preparation or is known to slow gastrointestinal motility (eg, opioids, anticholinergics, aspirin) or may cause a delayed onset of symptoms (eg, acetaminophen, colchicine, hepatotoxic mushrooms). After that time, the patient may be

discharged if no symptoms have developed. Before discharge, psychiatric evaluation should be performed to assess suicide risk. Intentional ingestions in adolescents should raise the possibility of unwanted pregnancy or sexual abuse.

THE SYMPTOMATIC PATIENT

In symptomatic patients, treatment of life-threatening complications takes precedence over in-depth diagnostic evaluation. Patients with mild symptoms may deteriorate rapidly, which is why all potentially significant exposures should be observed in an acute care facility. The following complications may occur, depending on the type of poisoning.

COMA

► Assessment & Complications

Coma is commonly associated with ingestion of large doses of antihistamines (eg, diphenhydramine), benzodiazepines and other sedative-hypnotic drugs, ethanol, opioids, anti-psychotic drugs, or antidepressants. The most common cause of death in comatose patients is respiratory failure, which may occur abruptly. Pulmonary aspiration of gastric contents may also occur, especially in victims who are deeply obtunded or convulsing. Hypoxia and hypoventilation may cause or aggravate hypotension, arrhythmias, and seizures. Thus, protection of the airway and assisted ventilation are the most important treatment measures for any poisoned patient.

► Treatment

A. Emergency Management

The initial emergency management of coma can be remembered by the mnemonic *ABCD*, for Airway, Breathing, Circulation, and Drugs (dextrose, thiamine, and naloxone or flumazenil), respectively.

1. Airway—Establish a patent airway by positioning, suction, or insertion of an artificial nasal or oropharyngeal airway. If the patient is deeply comatose or if airway

reflexes are depressed, perform endotracheal intubation. These airway interventions may not be necessary if the patient is intoxicated by an opioid or a benzodiazepine and responds to intravenous naloxone or flumazenil.

2. Breathing—Clinically assess the quality and depth of respiration and provide assistance, if necessary, with a bag-valve-mask device or mechanical ventilator. Administer supplemental oxygen, if needed. The arterial or venous blood CO₂ tension, or noninvasive end-tidal CO₂ monitoring, is useful in determining the adequacy of ventilation. The arterial blood PO₂ determination may reveal hypoxemia, which may be caused by respiratory depression, bronchospasm, pulmonary aspiration, or noncardiogenic pulmonary edema. Pulse oximetry provides an assessment of oxygenation, but is not reliable in patients with methemoglobinemia or carbon monoxide poisoning, unless a pulse oximetry device capable of detecting these forms of hemoglobin is used.

3. Circulation—Measure the pulse and blood pressure and estimate tissue perfusion (eg, by measurement of urinary output, skin signs, arterial blood pH). Place the patient on continuous ECG monitoring. Insert an intravenous line, and draw blood for glucose, electrolytes, serum creatinine and liver tests, and possible quantitative toxicologic testing.

4. Drugs—

A. DEXTROSE AND THIAMINE—Unless promptly treated, severe hypoglycemia can cause irreversible brain damage. Therefore, in all obtunded, comatose or convulsing patients, give 50% dextrose, 50–100 mL by intravenous bolus, unless a rapid point-of-care blood sugar test rules out hypoglycemia. In alcoholic or very malnourished patients who may have marginal thiamine stores, give thiamine 100 mg intramuscularly or in the intravenous fluids.

B. OPIOID ANTAGONISTS—Naloxone, 0.4–2 mg intravenously or 2–4 mg by intranasal spray, may reverse opioid-induced respiratory depression and coma. It is *often given empirically* to any comatose patient with depressed respirations. If opioid overdose is strongly suspected, give additional doses of naloxone (up to 5–10 mg may be required to reverse the effects of potent opioids). **Note:** Naloxone has a shorter duration of action (2–3 hours) than most common opioids; *repeated doses* may be required, and continuous observation for at least 3–4 hours after the last dose is mandatory.

C. FLUMAZENIL—Flumazenil, 0.2–0.5 mg intravenously, repeated as needed up to a maximum of 3 mg, may reverse benzodiazepine-induced coma. **Caution:** *In most circumstances, use of flumazenil is not advised as the potential risks outweigh its benefits.* Flumazenil should *not* be given if the patient has coingested a potential convulsant drug, is a user of high-dose benzodiazepines, or has a seizure disorder because its use in these circumstances may precipitate seizures. **Note:** Flumazenil has a short duration of effect (2–3 hours), and resedation requiring additional doses may occur.

HYPOTHERMIA

► Assessment & Complications

Hypothermia commonly accompanies coma due to opioids, ethanol, hypoglycemic agents, phenothiazines, barbiturates, benzodiazepines, and other sedative-hypnotics and central nervous system depressants. Hypothermic patients may have a barely perceptible pulse and blood pressure. Hypothermia may cause or aggravate hypotension, which will not reverse until the temperature is normalized.

► Treatment

Treatment of hypothermia is discussed in Chapter 37. Gradual rewarming is preferred unless the patient is in cardiac arrest.

HYPOTENSION

► Assessment & Complications

Hypotension may be due to poisoning by many different drugs, including antihypertensives, beta-blockers, calcium channel blockers, disulfiram (ethanol interaction), iron, trazodone, quetiapine, and other antipsychotic agents and antidepressants. Poisons causing hypotension include cyanide, carbon monoxide, hydrogen sulfide, aluminum or zinc phosphide, arsenic, and certain mushrooms.

Hypotension in the poisoned or drug-overdosed patient may be caused by venous or arteriolar vasodilation, hypovolemia, depressed cardiac contractility, or a combination of these effects.

► Treatment

Most hypotensive poisoned patients respond to empiric treatment with repeated 200 mL intravenous boluses of 0.9% saline or other isotonic crystalloid up to a total of 1–2 L; much larger amounts may be needed if the victim is profoundly volume depleted (eg, as with massive diarrhea due to *Amanita phalloides* mushroom poisoning). Monitoring the central venous pressure (CVP) can help determine whether further fluid therapy is needed. Consider bedside cardiac ultrasound or pulmonary artery catheterization (or both) to assess CVP. If fluid therapy is not successful after adequate volume replacement, give dopamine or norepinephrine by intravenous infusion.

Hypotension caused by certain toxins may respond to specific treatment. For hypotension caused by overdoses of tricyclic antidepressants or other sodium channel blockers, administer sodium bicarbonate, 50–100 mEq by intravenous bolus injection. Norepinephrine 4–8 mcg/min by intravenous infusion is more effective than dopamine in some patients with overdoses of tricyclic antidepressants or of drugs with predominantly vasodilating effects. For beta-blocker overdose, glucagon (5–10 mg intravenously) may be of value. For calcium channel blocker overdose, administer calcium chloride, 1–2 g intravenously (repeated doses may be necessary; doses of 5–10 g and more have been given in some cases). High-dose insulin (0.5–1 unit/kg/h intravenously) euglycemic therapy may also be used

(see the sections Beta-Adrenergic Blockers and Calcium Channel Blockers, below). Intralipid 20% lipid emulsion has been reported to improve hemodynamics in some cases of intoxication by highly lipid-soluble drugs such as bupivacaine, bupropion, clomipramine, and verapamil. Intravenous methylene blue and extracorporeal membrane oxygenation (ECMO) have been employed in a few refractory cases; ECMO may offer temporary hemodynamic stabilization while the offending drug is eliminated.

Mycyk MB. Extracorporeal membrane oxygenation shows promise for treatment of poisoning some of the time: the challenge to do better by aiming higher. Crit Care Med. 2020;48:1235. [PMID: 32697497]

Nafea OE et al. Comparative effectiveness of methylene blue versus intravenous lipid emulsion in a rodent model of amlodipine toxicity. Clin Toxicol (Phila). 2019;57:784. [PMID: 30729824]

Weiner L et al. Clinical utility of venoarterial-extracorporeal membrane oxygenation (VA-ECMO) in patients with drug-induced cardiogenic shock: a retrospective study of the Extracorporeal Life Support Organizations' ECMO case registry. Clin Toxicol (Phila). 2020;58:705. [PMID: 31617764]

HYPERTENSION

▶ Assessment & Complications

Hypertension may be due to poisoning with amphetamines and synthetic stimulants, anticholinergics, cocaine, performance-enhancing products (eg, containing caffeine, phenylephrine, ephedrine, or yohimbine), monoamine oxidase (MAO) inhibitors, and other drugs.

Severe hypertension (eg, diastolic blood pressure greater than 105–110 mm Hg in a person who does not have chronic hypertension) can result in acute intracranial hemorrhage, myocardial infarction, or aortic dissection.

▶ Treatment

Treat hypertension if the patient is symptomatic or if the diastolic pressure is higher than 105–110 mm Hg—especially if there is no prior history of hypertension.

Hypertensive patients who are agitated or anxious may benefit from a sedative (such as lorazepam, 2–3 mg intravenously) or an antipsychotic drug (eg, haloperidol or olanzapine). For persistent hypertension, administer phenotolamine, 2–5 mg intravenously, or nitroprusside sodium, 0.25–8 mcg/kg/min intravenously. If excessive tachycardia is present, add esmolol, 25–100 mcg/kg/min intravenously, or labetalol, 0.2–0.3 mg/kg intravenously. **Caution:** Do not give beta-blockers alone, since doing so may paradoxically worsen hypertension in some cases as a result of unopposed alpha-adrenergic stimulation.

ARRHYTHMIAS

▶ Assessment & Complications

Arrhythmias may occur with a variety of drugs or toxins (Table 38–1). They may also occur as a result of hypoxia, metabolic acidosis, or electrolyte imbalance (eg, hyperkalemia, hypokalemia, hypomagnesemia, or hypocalcemia), or

Table 38–1. Common toxins or drugs causing arrhythmias (listed in alphabetical order).¹

Arrhythmia	Common Causes
Atrioventricular block	Beta-blockers, calcium channel blockers, class Ia antiarrhythmics (including quinidine), carbamazepine, clonidine, digitalis glycosides, lithium
QT interval prolongation and torsades de pointes	Arsenic, class Ia and class III antiarrhythmics, citalopram, droperidol, lithium, methadone, pentamidine, sertraline, sotalol, and many other drugs ²
Sinus bradycardia	Beta-blockers, calcium channel blockers, clonidine, digitalis glycosides, organophosphates
Sinus tachycardia	Beta-agonists (eg, albuterol), amphetamines, anticholinergics, antihistamines, caffeine, cocaine, pseudoephedrine, tricyclic and other antidepressants
Ventricular premature beats and ventricular tachycardia	Amphetamines, cocaine, ephedrine, caffeine, chlorinated or fluorinated hydrocarbons, digoxin, aconite (found in some Chinese herbal preparations), fluoride, theophylline. QT prolongation can lead to atypical ventricular tachycardia (torsades de pointes)
Wide QRS complex	Class Ia and class IC antiarrhythmics, phenothiazines (eg, thioridazine), potassium (hyperkalemia), propranolol, tricyclic antidepressants, bupropion, lamotrigine, diphenhydramine (severe overdose)

¹Arrhythmias may also occur as a result of hypoxia, metabolic acidosis, or electrolyte imbalance (eg, hyperkalemia or hypokalemia, hypocalcemia, hypomagnesemia).

²<https://crediblemeds.org/>

following exposure to chlorinated solvents or chloral hydrate overdose. Atypical ventricular tachycardia (torsades de pointes) is often associated with drugs that prolong the QT interval.

▶ Treatment

Hypoxia or electrolyte imbalance should be sought and treated. If ventricular arrhythmias persist, administer lidocaine or amiodarone at usual antiarrhythmic doses. **Note:** Wide QRS complex tachycardia in the setting of tricyclic antidepressant overdose (or diphenhydramine or class Ia antiarrhythmic drugs) should be treated with sodium bicarbonate, 50–100 mEq intravenously by bolus infusion.

Caution: In such cases, avoid class Ia antiarrhythmic agents (eg, procainamide, disopyramide) and amiodarone, which may aggravate arrhythmias caused by tricyclic antidepressants. Torsades de pointes associated with prolonged QT interval may respond to intravenous magnesium (2 g

intravenously over 2 minutes) or overdrive pacing. Treat digitalis-induced arrhythmias with digoxin-specific antibodies.

For tachyarrhythmias induced by chlorinated solvents, chloral hydrate, Freons, or sympathomimetic agents, use propranolol or esmolol (see doses given above in Hypertension section).

Shakeer SK et al. Chloral hydrate overdose survived after cardiac arrest with excellent response to intravenous β -blocker. *Oman Med J*. 2019;34:244. [PMID: 31110633]

SEIZURES

► Assessment & Complications

Seizures may be caused by many poisons and drugs, including amphetamines, antidepressants (especially tricyclic antidepressants, bupropion, and venlafaxine), antihistamines (especially diphenhydramine), antipsychotics, camphor, synthetic cannabinoids and cathinones, cocaine, isoniazid (INH), chlorinated insecticides, piperazines, tramadol, and theophylline. The onset of seizures may be delayed for up to 18–24 hours after extended-released bupropion overdose.

Seizures may also be caused by hypoxia, hypoglycemia, hypocalcemia, hyponatremia, withdrawal from alcohol or sedative-hypnotics, head trauma, central nervous system infection, or idiopathic epilepsy.

Prolonged or repeated seizures may lead to hypoxia, metabolic acidosis, hyperthermia, and rhabdomyolysis.

► Treatment

Administer lorazepam, 2–3 mg, or diazepam, 5–10 mg, intravenously, or—if intravenous access is not immediately available—midazolam, 5–10 mg intramuscularly. If convulsions continue, administer phenobarbital, 15–20 mg/kg slowly intravenously over no less than 30 minutes. (For drug-induced seizures, phenobarbital is preferred over phenytoin or levetiracetam.) Propofol infusion has also been reported effective for some resistant drug-induced seizures.

Seizures due to a few drugs and toxins may require antidotes or other specific therapies (as listed in Table 38–2).

Park HR et al. Endosulfan-induced prolonged super-refractory status epilepticus. *J Epilepsy Res*. 2018;8:93. [PMID: 30809504]

HYPERTHERMIA

► Assessment & Complications

Hyperthermia may be associated with poisoning by amphetamines and other synthetic stimulants (cathinones, piperazines), atropine and other anticholinergic drugs, cocaine, salicylates, strychnine, 2,4-dinitrophenol, tricyclic antidepressants, and various other medications. Overdoses of serotonin reuptake inhibitors (eg, fluoxetine, paroxetine, sertraline) or their use in a patient taking an MAO

Table 38–2. Seizures related to toxins or drugs requiring special consideration (listed in alphabetical order).¹

Toxin or Drug	Comments
Isoniazid	Administer pyridoxine.
Lithium	May indicate need for hemodialysis.
Methylenedioxymethamphetamine (MDMA; "Ecstasy")	Seizures may also be due to hyponatremia or hyperthermia.
Organophosphates	Administer pralidoxime (2-PAM) and atropine in addition to usual anticonvulsants.
Strychnine	"Seizures" are actually spinally mediated muscle spasms and usually require neuromuscular paralysis and mechanical ventilation.
Theophylline	Seizures indicate need for hemodialysis.
Tricyclic antidepressants	Hyperthermia and cardiotoxicity are common complications of repeated seizures; paralyze early with neuromuscular blockers to reduce muscular hyperactivity.

¹See text for dosages.

inhibitor may cause agitation, hyperactivity, myoclonus, and hyperthermia ("serotonin syndrome"). Antipsychotic agents can cause rigidity and hyperthermia (neuroleptic malignant syndrome [NMS]). (See Chapter 25.) Malignant hyperthermia is a rare disorder associated with general anesthetic agents.

Hyperthermia is a rapidly life-threatening complication. Severe hyperthermia (temperature higher than 40–41°C) can rapidly cause brain damage and multiorgan failure, including rhabdomyolysis, acute kidney injury, and coagulopathy (see Chapter 37).

► Treatment

Treat hyperthermia aggressively by removing the patient's clothing, spraying the skin with tepid water, and high-volume fanning. Alternatively, the patient can be placed in an ice water bath (not simply applying ice to selected surfaces). If external cooling is not rapidly effective, as shown by a normal rectal temperature within 30–40 minutes, or if there is significant muscle rigidity or hyperactivity, induce neuromuscular paralysis with a nondepolarizing neuromuscular blocker (eg, rocuronium, vecuronium). Once paralyzed, the patient must be intubated and mechanically ventilated and sedated. While the patient is paralyzed, the absence of visible muscular convulsive movements may give the false impression that brain seizure activity has ceased; bedside electroencephalography may be useful in recognizing continued nonconvulsive seizures.

Dantrolene (2–5 mg/kg intravenously) may be effective for hyperthermia associated with muscle rigidity that does not respond to neuromuscular blockade (ie, malignant

hyperthermia). Bromocriptine, 2.5–7.5 mg orally daily, has been recommended for neuroleptic malignant syndrome. Cyproheptadine, 4 mg orally every hour for three or four doses, or chlorpromazine, 25 mg intravenously or 50 mg intramuscularly, has been used to treat serotonin syndrome.

Kopek KT et al. Dinitrophenol (DNP) fatality associated with a falsely elevated salicylate level: a case report with verification of laboratory cross reactivity. *J Med Toxicol*. 2018;14:323. [PMID: 30051204]

Tormoehlen LM et al. Neuroleptic malignant syndrome and serotonin syndrome. *Handb Clin Neurol*. 2018;157:663. [PMID: 30459031]

Van Schoor J et al. Dantrolene is not the answer to 2,4-dinitrophenol poisoning: more heated debate. *BMJ Case Rep*. 2018;11:e225323. [PMID: 30573533]

ANTIDOTES & OTHER TREATMENT

ANTIDOTES

Give an antidote (if available) when there is reasonable certainty of a specific diagnosis (Table 38–3). Be aware that some antidotes themselves may have serious side effects.

Table 38–3. Some toxic agents for which there are specific antidotes (listed in alphabetical order).¹

Toxic Agent	Specific Antidote
Acetaminophen	N-Acetylcysteine
Anticholinergics (eg, atropine)	Physostigmine
Anticholinesterases (eg, organophosphate pesticides)	Atropine and pralidoxime (2-PAM)
Benzodiazepines	Flumazenil (rarely used) ²
Carbon monoxide	Oxygen (hyperbaric oxygen of uncertain benefit)
Cyanide	Sodium nitrite, sodium thiosulfate; hydroxocobalamin
Digitalis glycosides	Digoxin-specific Fab antibodies
Heavy metals (eg, lead, mercury, iron) and arsenic	Specific chelating agents
Isoniazid	Pyridoxine (vitamin B ₆)
Methanol, ethylene glycol	Ethanol (ethyl alcohol) or fomepizole (4-methylpyrazole)
Opioids	Naloxone, naloxefene
Snake venom	Specific antivenin
Sulfonylurea oral hypoglycemic drugs	Glucose, octreotide

¹See text for indications and dosages.

²May induce seizures in patients with preexisting seizure disorder, benzodiazepine addiction, or concomitant tricyclic antidepressant or other convulsant overdose. If seizures occur, diazepam and other benzodiazepine anticonvulsants will not be effective. As with naloxone, the duration of action of flumazenil is short (2–3 hours) and sedation may occur, requiring repeated doses.

The indications and dosages for specific antidotes are discussed in the respective sections for specific toxins.

Dart RC et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. *Ann Emerg Med*. 2018;71:314. [PMID: 28669553]

DECONTAMINATION OF THE SKIN

Corrosive agents rapidly injure the skin and eyes and must be removed immediately. In addition, many toxins are readily absorbed through the skin, and systemic absorption can be prevented only by rapid action.

Wash the affected areas with copious quantities of lukewarm water or saline, taking care to limit exposure to health care providers. Wash carefully behind the ears, under the nails, and in skin folds. For oily substances (eg, pesticides), wash the skin at least twice with plain soap and shampoo the hair. Specific decontaminating solutions or solvents (eg, alcohol) are rarely indicated and in some cases may paradoxically enhance absorption. For exposure to chemical warfare poisons such as nerve agents or vesicants, some authorities recommend use of a dilute hypochlorite solution (household bleach diluted 1:10 with water), but not in the eyes.

DECONTAMINATION OF THE EYES

Act quickly to prevent serious damage. Flush the eyes with copious amounts of saline or water. (If available, instill local anesthetic drops in the eye before beginning irrigation.) Remove contact lenses if present. Lift the tarsal conjunctiva to look for undissolved particles and to facilitate irrigation. Continue irrigation for 15 minutes or until each eye has been irrigated with at least 1 L of solution. If the toxin is an acid or a base, check the pH of the tears after irrigation, and continue irrigation until the pH is between 6 and 8. An amphoteric decontamination solution (Diphofuterine, Prevor) is used in some countries for treatment of alkali injuries to the eye.

After irrigation is complete, perform a careful examination of the eye, using fluorescein and a slit lamp or Wood lamp to identify areas of corneal injury. Patients with serious conjunctival or corneal injury should be immediately referred to an ophthalmologist.

GASTROINTESTINAL DECONTAMINATION

Removal of ingested poisons by induced emesis or gastric lavage was a routine part of emergency treatment for decades. However, *prospective randomized studies have failed to demonstrate improved clinical outcome after gastric emptying*. For small or moderate ingestions of most substances, toxicologists often recommend oral activated charcoal alone without prior gastric emptying; in some cases, when the interval after ingestion has been more than 1–2 hours and the ingestion is non-life-threatening, even charcoal is withheld (eg, if the estimated benefit is outweighed by the potential risk of pulmonary aspiration of charcoal). Exceptions are large ingestions of

anticholinergic compounds and salicylates, which often delay gastric emptying, and ingestion of sustained-release or enteric-coated tablets, which may remain intact for several hours. In these cases, delayed gut decontamination may be indicated.

Gastric emptying is not generally used for ingestion of corrosive agents or petroleum distillates, because further esophageal injury or pulmonary aspiration may result. However, in certain cases, removal of the toxin may be more important than concern over possible complications. Consult a medical toxicologist or regional poison control center (1-800-222-1222) for advice.

A. Activated Charcoal

Activated charcoal effectively adsorbs almost all drugs and poisons. Poorly adsorbed substances include iron, lithium, potassium, sodium, mineral acids, and alcohols.

1. Indications—Activated charcoal can be used for prompt adsorption of drugs or toxins in the stomach and intestine. However, evidence of benefit in clinical studies is lacking. Administration of charcoal, especially if mixed with sorbitol, can provoke vomiting, which could lead to pulmonary aspiration in an obtunded patient.

2. Contraindications—Activated charcoal should not be used for comatose or convulsing patients unless it can be given by gastric tube and the airway is first protected by a cuffed endotracheal tube. It is also contraindicated for patients with ileus or intestinal obstruction or those who have ingested corrosives for whom endoscopy is planned.

3. Technique—Administer activated charcoal, 60–100 g orally or via gastric tube, mixed in aqueous slurry. Repeated doses may be given to ensure gastrointestinal adsorption or to enhance elimination of some drugs.

B. Whole Bowel Irrigation

Whole bowel irrigation uses large volumes of a balanced polyethylene glycol-electrolyte solution to mechanically cleanse the entire intestinal tract. Because of the composition of the irrigating solution, there is no significant gain or loss of systemic fluids or electrolytes.

1. Indications—Whole bowel irrigation is particularly effective for massive iron ingestion in which intact tablets are visible on abdominal radiographs. It has also been used for ingestions of lithium, sustained-release and enteric-coated tablets, and swallowed drug-filled packets.

2. Contraindications—Do not use in patients with suspected intestinal obstruction. Use with caution in patients who are obtunded or have depressed airway protective reflexes.

3. Technique—Administer a balanced polyethylene glycol-electrolyte solution (CoLyte, GOLYTELY) into the stomach via gastric tube at a rate of 1–2 L/h until the rectal effluent is clear. This may take several hours. It is most effective when patients are able to sit on a commode to pass the intestinal contents.

C. Increased Drug Removal

1. Urinary manipulation—Forced diuresis is hazardous; the risk of complications (fluid overload, electrolyte imbalance) usually outweighs its benefits. Some drugs (eg, salicylates, phenobarbital) are more rapidly excreted with an alkaline urine. To alkalinize the urine, add 100 mEq (two ampules) of sodium bicarbonate to 1 L of 5% dextrose in 0.225% saline (¼ normal saline), and infuse this solution intravenously at a rate of about 150–200 mL/h. Acidification (sometimes promoted for amphetamines, phencyclidine) is *not* very effective and should not be used.

2. Hemodialysis—The indications for dialysis are as follows: (1) known or suspected potentially lethal amounts of a dialyzable drug (Table 38–4); (2) poisoning with deep coma, apnea, severe hypotension, fluid and electrolyte or acid-base disturbance, or extreme body temperature changes that cannot be corrected by conventional measures; or (3) poisoning in patients with severe kidney, cardiac, pulmonary, or hepatic disease who will not be able to eliminate toxin by the usual mechanisms.

Continuous renal replacement therapy (including continuous venovenous hemodiafiltration and similar techniques) is of uncertain benefit for elimination of most poisons but has the advantage of gradual removal of the toxin and correction of any accompanying acidosis. Its use has been reported in the management of a variety of poisonings, including lithium intoxication.

3. Repeat-dose charcoal—Repeated doses of activated charcoal, 20–30 g orally or via gastric tube every 3–4 hours,

Table 38–4. Recommended use of hemodialysis in poisoning (listed in alphabetical order).¹

Poison	Common Indications ¹
Carbamazepine	Seizures, severe cardiotoxicity; serum level > 60 mg/L
Ethylene glycol	Acidosis, serum level > 50 mg/dL
Lithium	Severe symptoms; level > 4–5 mEq/L, especially if kidney impairment Note: dialysis of uncertain value; consult with medical toxicologist
Methanol	Acidosis, serum level > 50 mg/dL
Phenobarbital	Intractable hypotension, acidosis despite maximal supportive care
Salicylate	Severe acidosis, CNS symptoms, serum level > 100 mg/dL (acute overdose) or > 60 mg/dL (chronic intoxication)
Theophylline	Serum level > 90–100 mg/L (acute) or seizures and serum level > 40–60 mg/L (chronic)
Valproic acid	Serum level > 900–1000 mg/L or deep coma, severe acidosis

¹See text for further discussion of indications.
CNS, central nervous system.

may hasten elimination of some drugs (eg, phenytoin, carbamazepine, dapsone) by absorbing drugs excreted into the gut lumen ("gut dialysis"). However, clinical studies have failed to prove better outcome using repeat dose charcoal. Sorbitol or other cathartics should *not* be used with each dose, or else the resulting large stool volumes may lead to dehydration or hypernatremia.

Campion GH et al. Extracorporeal treatments in poisonings from four non-traditionally dialysed toxins (acetaminophen, digoxin, opioids and tricyclic antidepressants): a combined single-centre and national study. *Basic Clin Pharmacol Toxicol*. 2019;124:341. [PMID: 30248244]

Ghannoum M et al. Use of extracorporeal treatments in the management of poisonings. *Kidney Int*. 2018;94:682. [PMID: 29958694]

Harbord N. Common toxicodromes and the role of extracorporeal detoxification. *Adv Chronic Kidney Dis*. 2020;27:11. [PMID: 32146996]

Zellner T et al. The use of activated charcoal to treat intoxications. *Dtsch Arztebl Int*. 2019;116:311. [PMID: 31219028]

DIAGNOSIS OF POISONING

The identity of the ingested substance or substances is usually known, but occasionally a comatose patient is found with an unlabeled container or the patient is unable or unwilling to give a coherent history. By performing a directed physical examination and ordering common clinical laboratory tests, the clinician can often make a tentative diagnosis that may allow empiric interventions or may suggest specific toxicologic tests.

Physical Examination

Important diagnostic variables in the physical examination include blood pressure, pulse rate, temperature, pupil size, sweating, muscle tone, level of consciousness, and the presence or absence of peristaltic activity. Poisonings may present with one or more of the following common syndromes.

A. Sympathomimetic Syndrome

The blood pressure and pulse rate are elevated, though with severe hypertension reflex bradycardia may occur. The temperature is often elevated, pupils are dilated, and the skin is sweaty, though mucous membranes are dry. Patients are usually agitated, anxious, or frankly psychotic.

Examples: Amphetamines, cocaine, ephedrine, pseudoephedrine, synthetic cathinones and cannabinoids.

B. Sympatholytic Syndrome

The blood pressure and pulse rate are decreased, and body temperature is low. The pupils are small or even pinpoint. Patients are usually obtunded or comatose.

Examples: Barbiturates, benzodiazepines and other sedative hypnotics, gamma-hydroxybutyrate (GHB), clonidine and related antihypertensives, ethanol, opioids.

C. Cholinergic Syndrome

Stimulation of muscarinic receptors causes bradycardia, miosis (constricted pupils), sweating, and hyperperistalsis as well as bronchorrhea, wheezing, excessive salivation, and urinary incontinence. Nicotinic receptor stimulation may produce initial hypertension and tachycardia as well as fasciculations and muscle weakness. Patients are usually agitated and anxious.

Examples: Carbamates, nicotine, organophosphates (including nerve agents), physostigmine.

D. Anticholinergic Syndrome

Tachycardia with mild hypertension is common, and the body temperature is often elevated. Pupils are widely dilated. The skin is flushed, hot, and dry. Peristalsis is decreased, and urinary retention is common. Patients may have myoclonic jerking or choreoathetoid movements. Agitated delirium is frequently seen, and severe hyperthermia may occur.

Examples: Atropine, scopolamine, other naturally occurring and pharmaceutical anticholinergics, antihistamines, tricyclic antidepressants.

Laboratory Tests

The following clinical laboratory tests are recommended for screening of the overdosed patient: measured serum osmolality and calculated osmol gap (if toxic alcohol ingestion is in the differential diagnosis), electrolytes and anion gap, glucose, creatinine, blood urea nitrogen (BUN), creatine kinase (CK), urinalysis (eg, oxalate crystals with ethylene glycol poisoning, myoglobinuria with rhabdomyolysis), and electrocardiography. Quantitative serum acetaminophen and ethanol levels should be determined in all patients with drug overdoses as well as a serum or urine pregnancy test when appropriate.

A. Osmol Gap

The osmol gap (Table 38–5) is increased in the presence of large quantities of low-molecular-weight substances, most

Table 38–5. Use of the osmol gap in toxicology.

The osmol gap (Delta osm) is determined by subtracting the calculated serum osmolality from the measured serum osmolality.

$$\text{Calculated osmolality} = 2[\text{Na}^+(\text{mEq/L})] + \frac{\text{Glucose}(\text{mg/dL})}{18} + \frac{\text{BUN}(\text{mg/dL})}{2.8}$$

$$\text{Delta osm} = \text{Measured osmolality} - \text{Calculated osmolality} = 0 \pm 10$$

Serum osmolality may be increased by contributions of exogenous substances such as alcohols and other low-molecular-weight substances. Since these substances are not included in the calculated osmolality, there will be a gap proportionate to their serum concentration. Contact a medical toxicologist or poison control center for assistance in calculating and interpreting the osmol gap.

commonly ethanol. Other common poisons associated with increased osmol gap are acetone, ethylene glycol, isopropyl alcohol, methanol, and propylene glycol. **Note:** Severe alcoholic ketoacidosis and diabetic ketoacidosis can also cause an elevated osmol gap resulting from the production of ketones and other low-molecular-weight substances.

B. Anion Gap

Metabolic acidosis associated with an elevated anion gap is usually due to an accumulation of lactic acid or other acids (see Chapter 21). Common causes of elevated anion gap in poisoning include carbon monoxide, cyanide, ethylene glycol, propylene glycol, medicinal iron, INH, methanol, metformin, ibuprofen, and salicylates. Massive acetaminophen overdose can cause early-onset anion gap metabolic acidosis.

The osmol gap should also be checked; combined elevated anion and osmol gaps suggests poisoning by methanol or ethylene glycol, though this may also occur in patients with diabetic ketoacidosis and alcoholic ketoacidosis.

C. Toxicology Laboratory Testing

A comprehensive toxicology screen is of little value in the initial care of the poisoned patient because results usually do not return in time to influence clinical management. Specific quantitative levels of certain drugs may be extremely helpful (Table 38–6), however, especially if specific antidotes or interventions (eg, dialysis) would be indicated based on the results.

Many hospitals can perform a quick but limited urine screen for “drugs of abuse” (typically these screens include only opiates, amphetamines, and cocaine, and some add benzodiazepines, barbiturates, methadone, oxycodone, phencyclidine, and tetrahydrocannabinol [marijuana]). There are numerous *false-positive* and *false-negative* results. For example, synthetic opioids, such as fentanyl, oxycodone, and methadone, are often not detected by routine opiate immunoassays.

► Abdominal Imaging

A plain film (or CT scan) of the abdomen may reveal radiopaque iron tablets, drug-filled condoms, or other toxic material. Studies suggest that few tablets are predictably visible (eg, ferrous sulfate, sodium chloride, calcium carbonate, and potassium chloride). Thus, the radiograph is useful only if abnormal.

► When to Refer

Consultation with a regional poison control center (1-800-222-1222) or a medical toxicologist is recommended when the diagnosis is uncertain; there are questions about what laboratory tests to order; when dialysis is being considered to remove the drug or poison; or when advice is needed regarding the indications, dose, and side effects of antidotes.

► When to Admit

- The patient has symptoms and signs of intoxication that are not expected to clear within a 6- to 8-hour observation period.

Table 38–6. Specific quantitative levels and potential therapeutic interventions (listed in alphabetical order).¹

Drug or Toxin	Treatment
Acetaminophen	Specific antidote (<i>N</i> -acetylcysteine) based on serum level
Carbon monoxide	High carboxyhemoglobin level indicates need for 100% oxygen, consideration of hyperbaric oxygen
Carbamazepine	High level may indicate need for hemodialysis
Digoxin	On basis of serum digoxin level and severity of clinical presentation, treatment with Fab antibody fragments (eg, DigiFab) may be indicated
Ethanol	Low serum level may suggest nonalcoholic cause of coma (eg, trauma, other drugs, other alcohols); serum ethanol may also be useful in monitoring ethanol therapy for methanol or ethylene glycol poisoning
Iron	Level may indicate need for chelation with deferoxamine
Lithium	Serum levels can guide decision to institute hemodialysis
Methanol, ethylene glycol	Acidosis, high levels indicate need for hemodialysis, therapy with ethanol or fomepizole
Methemoglobin	Methemoglobinemia can be treated with methylene blue intravenously
Salicylates	High level may indicate need for hemodialysis, alkaline diuresis
Theophylline	Immediate hemodialysis or hemoperfusion may be indicated based on serum level
Valproic acid	Elevated levels may indicate need to consider hemodialysis or L-carnitine therapy, or both

¹Some drugs or toxins may have profound and irreversible toxicity unless rapid and specific management is provided outside of routine supportive care. For these agents, laboratory testing may provide the serum level or other evidence required for administering a specific antidote or arranging for hemodialysis.

- Delayed absorption of the drug might be predicted to cause a later onset of serious symptoms (eg, after ingestion of a sustained-release product).
- Continued administration of an antidote is required (eg, *N*-acetylcysteine for acetaminophen overdose).
- Psychiatric or social services evaluation is needed for suicide attempt or suspected drug abuse.

SELECTED POISONINGS

ACETAMINOPHEN

Acetaminophen (paracetamol in the United Kingdom, Europe) is a common analgesic found in many nonprescription and prescription products. After absorption, it is metabolized mainly by glucuronidation and sulfation, with a small fraction metabolized via the P450 mixed-function oxidase system (2E1) to a highly toxic reactive intermediate. This toxic intermediate is normally detoxified by cellular glutathione. With acute acetaminophen overdose (greater than 150–200 mg/kg, or 8–10 g in an average adult), hepatocellular glutathione is depleted and the reactive intermediate attacks other cell proteins, causing necrosis. Patients with enhanced P450 2E1 activity, such as those who chronically abuse alcohol and patients taking INH, are at increased risk for developing hepatotoxicity. Hepatic toxicity may also occur after overuse of acetaminophen—eg, as a result of taking two or three acetaminophen-containing products concurrently or exceeding the recommended maximum dose of 4 g/day for several days. The amount of acetaminophen in US oral prescription combination products (eg, hydrocodone/acetaminophen) is limited by the FDA to no more than 325 mg per tablet.

Clinical Findings

Shortly after ingestion, patients may have nausea or vomiting, but there are usually no other signs of toxicity until 24–48 hours after ingestion, when hepatic aminotransferase levels begin to increase. With severe poisoning, fulminant

hepatic necrosis may occur, resulting in jaundice, hepatic encephalopathy, acute kidney injury, and death. Rarely, massive ingestion (eg, serum levels greater than 500–1000 mg/L [33–66 mmol/L]) can cause early onset of acute coma, seizures, hypotension, and metabolic acidosis unrelated to hepatic injury.

The diagnosis after acute overdose is based on measurement of the serum acetaminophen level. Plot the serum level versus the time since ingestion on the acetaminophen nomogram shown in Figure 38–1. Ingestion of sustained-release products or coingestion of an anticholinergic agent, salicylate, or opioid drug may cause delayed elevation of serum levels, which can make it difficult to interpret the nomogram. In addition, the nomogram cannot be used after chronic or staggered overdose.

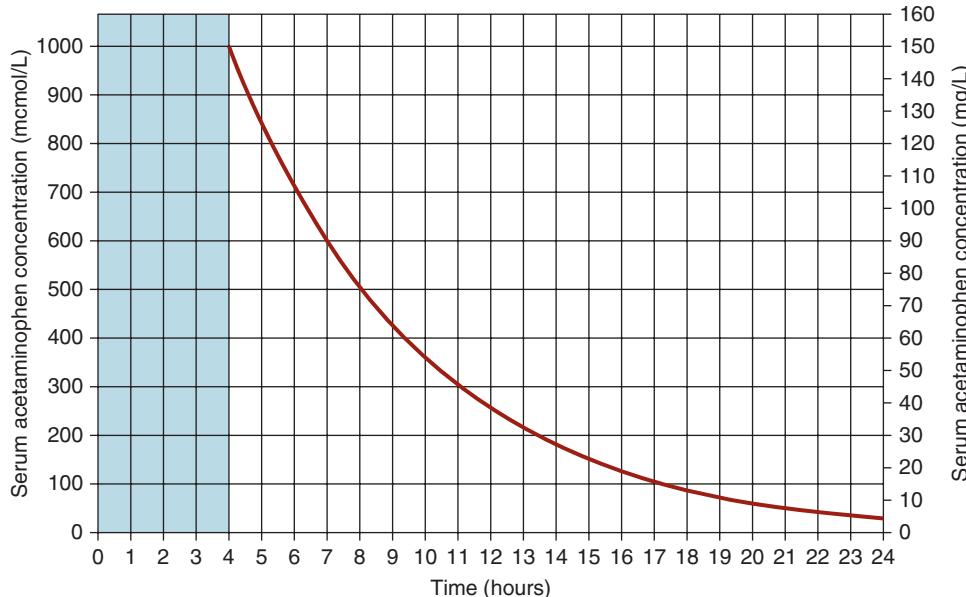
Treatment

A. Emergency and Supportive Measures

Administer activated charcoal if it can be given within 1–2 hours of the ingestion. Although charcoal may interfere with absorption of the oral preparation of the antidote *N*-acetylcysteine, this is not considered clinically significant.

B. Specific Treatment

If the serum or plasma acetaminophen level falls above the line on the nomogram (Figure 38–1), treatment with *N*-acetylcysteine is indicated; it can be given orally or intravenously. Oral treatment begins with a loading dose of *N*-acetylcysteine, 140 mg/kg, followed by 70 mg/kg every 4 hours. Dilute the solution to about 5% with water,



▲ Figure 38–1. Nomogram for prediction of acetaminophen hepatotoxicity following acute overdosage. Patients with serum levels above the line after acute overdose should receive antidotal treatment. (Adapted, with permission, from Daly FF et al. Guidelines for the management of paracetamol poisoning in Australia and New Zealand—explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian Poisons Information Centres. Med J Austr. 2008;188:296. © Copyright 2008 The Medical Journal of Australia. By permission from John Wiley & Sons.)

juice, or soda. If vomiting interferes with oral *N*-acetylcysteine administration, consider giving the antidote intravenously. The conventional oral *N*-acetylcysteine protocol in the United States calls for 72 hours of treatment. However, other regimens have demonstrated equivalent success with 20–48 hours of treatment.

The FDA-approved 21-hour intravenous regimen of acetylcysteine (Acetadote) calls for a loading dose of 150 mg/kg given intravenously over 60 minutes, followed by a 4-hour infusion of 50 mg/kg, and a 16-hour infusion of 100 mg/kg. Very large ingestions of acetaminophen (reported ingestions of more than 30 g or if the measured serum acetaminophen level is greater than twice the nomogram line) may require higher dose of *N*-acetylcysteine, and providers should contact a regional poison control center or medical toxicologist for assistance.

Treatment with *N*-acetylcysteine is most effective if it is started within 8–10 hours after ingestion. Hemodialysis is rarely indicated, but might be needed in some patients with massive overdose.

Chiew AL et al. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev. 2018;2:CD003328. [PMID: 29473717]

Hendrickson RG. What is the most appropriate dose of *N*-acetylcysteine after massive acetaminophen overdose? Clin Toxicol (Phila). 2019;57:686. [PMID: 30777470]

Lucyk S. Calculated decisions: acetaminophen overdose and *N*-acetylcysteine (NAC) dosing. Emerg Med Pract. 2018;20:S3. [PMID: 29617550]

Woodhead K et al. BET 1: In paracetamol overdose, is oral *N*-acetylcysteine as effective as intravenous *N*-acetylcysteine? Emerg Med J. 2018;35:643. [PMID: 30249712]

ACIDS, CORROSIVE

The strong mineral acids exert primarily a local corrosive effect on the skin and mucous membranes. Symptoms include severe pain in the throat and upper gastrointestinal tract; bloody vomitus; difficulty in swallowing, breathing, and speaking; discoloration and destruction of skin and mucous membranes in and around the mouth; and shock. Severe systemic metabolic acidosis may occur both as a result of cellular injury and from systemic absorption of the acid.

Severe deep destructive tissue damage may occur after exposure to hydrofluoric acid because of the penetrating and highly toxic fluoride ion. Systemic hypocalcemia and hyperkalemia may also occur after fluoride absorption, even following skin exposure.

Inhalation of volatile acids, fumes, or gases such as chlorine, fluorine, bromine, or iodine causes severe irritation of the throat and larynx and may cause upper airway obstruction and noncardiogenic pulmonary edema.

Treatment

A. Ingestion

Dilute immediately by giving a glass (4–8 oz) of water to drink. Do not give bicarbonate or other neutralizing agents, and do not induce vomiting. Some experts recommend immediate cautious placement of a small flexible

gastric tube and removal of stomach contents followed by lavage, particularly if the corrosive is a liquid or has important systemic toxicity.

In symptomatic patients, perform flexible endoscopic esophagoscopy to determine the presence and extent of injury. CT scan or plain radiographs of the chest and abdomen may also reveal the extent of injury. Perforation, peritonitis, and major bleeding are indications for surgery. The use of corticosteroids to prevent stricture formation is controversial but may be indicated in select patient populations.

B. Skin Contact

Flood with water for 15 minutes. Use no chemical antidotes; the heat of the reaction may cause additional injury.

For hydrofluoric acid burns, apply 2.5% calcium gluconate gel (prepared by adding 3.5 g calcium gluconate to 5 oz of water-soluble surgical lubricant, eg, K-Y Jelly); then arrange immediate consultation with a plastic surgeon or other specialist. Binding of the fluoride ion may be achieved by injecting 0.5 mL of 5% calcium gluconate per square centimeter under the burned area. (Caution: Do not use calcium chloride.) Use of a Bier-block technique or intra-arterial infusion of calcium is sometimes required for extensive burns or those involving the nail bed; consult with a hand surgeon or poison control center (1-800-222-1222).

C. Eye Contact

Anesthetize the conjunctiva and corneal surfaces with topical local anesthetic drops (eg, proparacaine). Flood with water for 15 minutes, holding the eyelids open. Check pH with pH 6.0–8.0 test paper, and repeat irrigation, using 0.9% saline, until pH is near 7.0. Check for corneal damage with fluorescein and slit-lamp examination; consult an ophthalmologist about further treatment.

D. Inhalation

Remove from further exposure to fumes or gas. Check skin and clothing. Observe for and treat chemical pneumonitis or pulmonary edema.

Hoffman RS et al. Ingestion of caustic substances. N Engl J Med. 2020;382:1739. [PMID: 32348645]

Hoffman S et al. Dermal hydrofluoric acid toxicity case review: looks can be deceiving. J Emerg Nurs. 2021;47:28. [PMID: 33183770]

ALKALIES

The strong alkalies are common ingredients of some household cleaning compounds and may be suspected by their “soapy” texture. Those with alkalinity above pH 12.0 are particularly corrosive. Disk (or “button”) batteries are also a source. Alkalies cause liquefactive necrosis, which is deeply penetrating. Symptoms include burning pain in the upper gastrointestinal tract, nausea, vomiting, and difficulty in swallowing and breathing. Examination reveals destruction and edema of the affected skin and mucous

membranes and bloody vomitus and stools. Radiographs may reveal evidence of perforation or the presence of radiopaque disk batteries in the esophagus or lower gastrointestinal tract.

► Treatment

A. Ingestion

Dilute immediately with a glass of water. Do *not* induce emesis. Some gastroenterologists recommend immediate cautious placement of a small flexible gastric tube and removal of stomach contents followed by gastric lavage after ingestion of liquid caustic substances, in order to remove residual material. However, others argue that passage of a gastric tube is contraindicated due to the risk of perforation or reexposure of the esophagus to the corrosive material from vomiting around the tube.

Prompt endoscopy is recommended in symptomatic patients to evaluate the extent of damage; CT scanning may also aid in assessment. If a radiograph reveals ingested disk batteries lodged in the esophagus, immediate endoscopic removal is mandatory.

The use of corticosteroids to prevent stricture formation is controversial but may be indicated in select patient populations.

B. Skin Contact

Wash with running water until the skin no longer feels soapy. Relieve pain and treat shock.

C. Eye Contact

Anesthetize the conjunctival and corneal surfaces with topical anesthetic (eg, proparacaine). Irrigate with water or saline continuously for 20–30 minutes, holding the lids open. Amphoteric solutions may be more effective than water or saline and some are available in Europe (Diphofterine, Prevor). Check pH with pH test paper and repeat irrigation for additional 30-minute periods until the pH is near 7.0. Check for corneal damage with fluorescein and slit-lamp examination; consult an ophthalmologist for further treatment.

Bizrah M et al. An update on chemical eye burns. *Eye (Lond)*. 2019;33:1362. [PMID: 31086244]

Dohmlan CH et al. Chemical burns of the eye: the role of retinal injury and new therapeutic possibilities. *Cornea*. 2018;37:248. [PMID: 29135604]

Zhang X et al. Tractional Descemet's membrane detachment after ocular alkali burns: case reports and review of literature. *BMC Ophthalmol*. 2018;18:256. [PMID: 30249214]

tolerance. The onset of effects is most rapid after intravenous injection or smoking. Amphetamine derivatives and related drugs include methamphetamine ("crystal meth," "crank"), MDMA ("Ecstasy"), ephedrine ("herbal ecstasy"), and methcathinone ("cat" or "khat"). Methcathinone derivatives and related synthetic chemicals such as methylene-dioxypyrovalerone (MDPV) have become popular drugs of abuse and are often sold as purported "bath salts." Amphetamine-like reactions have also been reported after use of synthetic cannabinoids (eg, "Spice" and "K2"). Nonprescription medications and nutritional supplements may contain stimulant or sympathomimetic drugs such as ephedrine, yohimbine, or caffeine (see also Theophylline & Caffeine section).

► Clinical Findings

Presenting symptoms may include anxiety, tremulousness, tachycardia, hypertension, diaphoresis, dilated pupils, agitation, muscular hyperactivity, and psychosis. Muscle hyperactivity may lead to metabolic acidosis and rhabdomyolysis. In severe intoxication, seizures and hyperthermia may occur. Sustained or severe hypertension may result in intracranial hemorrhage, aortic dissection, or myocardial infarction; chronic use may cause cardiomyopathy. Ischemic colitis has been reported. Hyponatremia has been reported after MDMA use; the mechanism is not known but may involve excessive water intake, syndrome of inappropriate antidiuretic hormone (SIADH), or both.

The diagnosis is supported by finding amphetamines or the cocaine metabolite benzoylecgonine in the urine. Note that many drugs can give false-positive results on the immunoassay for amphetamines, and most synthetic stimulants do not react with the immunoassay, giving false-negative results.

► Treatment

A. Emergency and Supportive Measures

Maintain a patent airway and assist ventilation, if necessary. Treat seizures as described at the beginning of this chapter. Rapidly lower the body temperature in patients who are hyperthermic (temperature higher than 39–40°C). Give intravenous fluids to prevent myoglobinuric kidney injury in patients who have rhabdomyolysis.

B. Specific Treatment

Treat agitation, psychosis, or seizures with a benzodiazepine such as diazepam, 5–10 mg, or lorazepam, 2–3 mg intravenously. Add phenobarbital 15 mg/kg intravenously for persistent seizures. Treat hypertension with a vasodilator drug such as phentolamine (1–5 mg intravenously) or nitroprusside, or a combined alpha- and beta-adrenergic blocker such as labetalol (10–20 mg intravenously). Do *not* administer a pure beta-blocker such as propranolol alone, as this may result in paradoxical worsening of the hypertension as a result of unopposed alpha-adrenergic effects.

Treat tachycardia or tachyarrhythmias with a short-acting beta-blocker such as esmolol (25–100 mcg/min

AMPHETAMINES & COCAINE

Amphetamines and cocaine are widely abused for their euphorogenic and stimulant properties. Both drugs may be smoked, snorted, ingested, or injected. Amphetamines and cocaine produce central nervous system stimulation and a generalized increase in central and peripheral sympathetic activity. The toxic dose of each drug is highly variable and depends on the route of administration and individual

by intravenous infusion). Treat hyperthermia as described above. Treat hyponatremia as outlined in Chapter 21.

- Luethi D et al. Designer drugs: mechanism of action and adverse effects. *Arch Toxicol*. 2020;94:1085. [PMID: 32249347]
- Rahimi M et al. Predictive factors of mortality in acute amphetamine type stimulants poisoning: a review of 226 cases. *Emerg (Tehran)*. 2018;6:e1. [PMID: 29503826]
- Richards JR et al. Methamphetamine use and heart failure: prevalence, risk factors, and predictors. *Am J Emerg Med*. 2018;36:1423. [PMID: 29307766]
- Stockings E et al. Mortality among people with regular or problematic use of amphetamines: a systematic review and meta-analysis. *Addiction*. 2019;114:1738. [PMID: 31180607]

ANTICOAGULANTS

Warfarin and related compounds (including ingredients of many commercial rodenticides, the so-called superwarfarins such as brodifacoum, difenacoum, and related compounds) inhibit the normal clotting system by blocking hepatic synthesis of vitamin K-dependent clotting factors. After ingestion of “superwarfarins,” inhibition of clotting factor synthesis may persist for several weeks or even months after a single dose. Direct-acting oral anticoagulants (DOACs) include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, betrixaban, edoxaban, and rivaroxaban. Some of these, especially dabigatran, are largely eliminated by the kidney and may accumulate in patients with kidney dysfunction.

Excessive anticoagulation may cause hemoptysis, gross hematuria, bloody stools, hemorrhages into organs, widespread bruising, and bleeding into joint spaces.

Treatment

A. Emergency and Supportive Measures

Discontinue the drug at the first sign of gross bleeding, and determine the prothrombin time (international normalized ratio, INR). The prothrombin time is increased within 12–24 hours (peak 36–48 hours) after overdose of warfarin or “superwarfarins.” **Note:** DOACs (dabigatran, apixaban, betrixaban, edoxaban, and rivaroxaban) do not predictably alter routine coagulation studies (prothrombin time, partial thromboplastin time, and INR), and these tests are of limited use. Specialized coagulation studies including the hemaclot and ecarin clotting assay and the anti-factor Xa activity may be helpful but are not widely available.

If the patient has ingested an acute overdose, administer activated charcoal.

B. Specific Treatment

1. Warfarin—*In cases of warfarin and “superwarfarin” overdose, do not treat prophylactically with vitamin K—wait for evidence of anticoagulation (elevated prothrombin time).* See Table 14–21 for the management of INR above therapeutic range. Doses of vitamin K as high as 200 mg/day have been required after ingestion of “superwarfarins.” Give fresh-frozen plasma, prothrombin complex concentrate, or activated factor VII as needed to rapidly correct the coagulation factor deficit if there is serious bleeding. If

the patient is chronically anticoagulated and has strong medical indications for being maintained in that status (eg, prosthetic heart valve), give much smaller doses of vitamin K (1 mg orally) and fresh-frozen plasma (or both) to titrate to the desired prothrombin time. If the patient has ingested brodifacoum or a related superwarfarin, prolonged observation (over weeks) and repeated administration of large doses of vitamin K may be required.

2. Direct-acting oral anticoagulants—Vitamin K does not reverse the anticoagulant effects of the DOACs. **Idarucizumab** has been approved by the FDA for reversal of the thrombin inhibitor dabigatran; **andexanet** is approved for reversal of the factor Xa inhibitors apixaban, edoxaban, betrixaban, and rivaroxaban. If specific reversal agents are unavailable, evidence supports the use of prothrombin complex concentrates or activated prothrombin complex concentrates for reversal of factor Xa inhibitors.

Cuker A et al. Reversal of direct oral anticoagulants: guidance from the Anticoagulation Forum. *Am J Hematol*. 2019;94:697. [PMID: 30916798]

Dobesh PP et al. Antidotes for reversal of direct oral anticoagulants. *Pharmacol Ther*. 2019;204:107405. [PMID: 31521696]

Gunasekaran K et al. A review of the incidence diagnosis and treatment of spontaneous hemorrhage in patients treated with direct oral anticoagulants. *J Clin Med*. 2020;9:2984. [PMID: 32942757]

Korobey MJ et al. Efficacy of 4-factor prothrombin complex concentrates in factor Xa inhibitor-associated intracranial bleeding. *Neurocrit Care*. 2021;34:112. [PMID: 32430804]

ANTICONVULSANTS

Anticonvulsants (carbamazepine, phenytoin, valproic acid, and many newer agents) are widely used in the management of seizure disorders and some are also used for treatment of mood disorders or pain.

Phenytoin can be given orally or intravenously. Rapid intravenous injection of phenytoin can cause acute myocardial depression and cardiac arrest owing to the solvent propylene glycol (fosphenytoin does not contain this diluent). Chronic phenytoin intoxication can occur following only slightly increased doses because of zero-order kinetics and a small toxic-therapeutic window. Phenytoin intoxication can also occur following acute intentional or accidental overdose. The overdose syndrome is usually mild even with high serum levels. The most common manifestations are ataxia, nystagmus, and drowsiness. Choreoathetoid movements have been described.

Carbamazepine intoxication causes drowsiness, stupor and, with high levels, atrioventricular block, coma, and seizures. Dilated pupils and tachycardia are common. Toxicity may be seen with serum levels over 20 mg/L (85 mcg/L), although severe poisoning is usually associated with concentrations greater than 30–40 mg/L (127–169 mcg/L). Because of erratic and slow absorption, intoxication may progress over several hours to days.

Valproic acid intoxication produces a unique syndrome consisting of hypernatremia (from the sodium component of the salt), metabolic acidosis, hypocalcemia, elevated serum ammonia, and mild liver aminotransferase

elevation. Hypoglycemia may occur as a result of hepatic metabolic dysfunction. Coma with small pupils may be seen and can mimic opioid poisoning. Encephalopathy and cerebral edema can occur.

Gabapentin, levetiracetam, vigabatrin, and zonisamide generally cause somnolence, confusion, and dizziness; there is one case report of hypotension and bradycardia after a large overdose of levetiracetam. **Felbamate** can cause crystalluria and kidney injury after overdose and may cause idiosyncratic aplastic anemia with therapeutic use. **Lamotrigine, topiramate, and tiagabine** have been reported to cause seizures after overdose; lamotrigine has sodium channel-blocking properties and may cause QRS prolongation and heart block.

Treatment

A. Emergency and Supportive Measures

For recent ingestions, give activated charcoal orally or by gastric tube. For large ingestions of carbamazepine or valproic acid—especially of sustained-release formulations—consider whole bowel irrigation.

B. Specific Treatment

There are no specific antidotes. Naloxone was reported in several case reports to reverse sedation in valproic acid overdose. Carnitine may be useful in patients with valproic acid-induced hyperammonemia. Consider hemodialysis for massive intoxication with valproic acid or carbamazepine (eg, carbamazepine levels greater than 60 mg/L [254 mcg/L] or valproic acid levels greater than 800 mg/L [5544 mcg/L]).

- Alyaha B et al. Acute lamotrigine overdose: a systematic review of published adult and pediatric cases. *Clin Toxicol (Phila)*. 2018;56:81. [PMID: 28862044]
- Kalogera V et al. Patient survival after acute voluntary poisoning with a huge dose of oxcarbazepine and olanzapine. *Med Arch*. 2018;72:303. [PMID: 30515002]
- Yang X et al. Early hemoperfusion for emergency treatment of carbamazepine poisoning. *Am J Emerg Med*. 2018;36:926. [PMID: 29066188]

ANTIPSYCHOTIC DRUGS

Drugs in this group include “conventional” antipsychotics (eg, chlorpromazine, haloperidol, droperidol) and newer “atypical” antipsychotics (eg, risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole). While conventional drugs act mainly on CNS dopamine receptors, atypical drugs also interact with serotonin receptors.

Therapeutic doses of conventional phenothiazines (particularly chlorpromazine) induce drowsiness and mild orthostatic hypotension in as many as 50% of patients. Larger doses can cause obtundation, miosis, severe hypertension, tachycardia, convulsions, and coma. Abnormal cardiac conduction may occur, resulting in prolongation of QRS or QT intervals (or both) and ventricular arrhythmias. Among the atypical agents, quetiapine is more likely to cause coma and hypotension. Hypotension is probably

related to blockade of peripheral alpha-adrenergic receptors, causing vasodilatation.

With therapeutic or toxic doses, an acute extrapyramidal dystonic reaction may develop in some patients, with spasmotic contractions of the face and neck muscles, extensor rigidity of the back muscles, carpopedal spasm, and motor restlessness. This reaction is more common with haloperidol and other butyrophenones and less common with newer atypical antipsychotics. Severe rigidity accompanied by hyperthermia and metabolic acidosis (“**neuroleptic malignant syndrome**”) may occasionally occur and is life-threatening (see Chapter 25). Atypical antipsychotics have also been associated with weight gain and diabetes mellitus, including diabetic ketoacidosis.

Treatment

A. Emergency and Supportive Measures

Administer activated charcoal for large or recent ingestions. For severe hypotension, treatment with intravenous fluids and vasopressor agents may be necessary. Treat hyperthermia as outlined. Maintain ECG monitoring.

B. Specific Treatment

Hypotension often responds to intravenous saline boluses; cardiac arrhythmias associated with widened QRS intervals on the ECG may respond to intravenous sodium bicarbonate as is given for tricyclic antidepressant overdoses. Prolongation of the QT interval and torsades de pointes are usually treated with intravenous magnesium or overdrive pacing.

For extrapyramidal signs, give diphenhydramine, 0.5–1 mg/kg intravenously, or benztrapine mesylate, 0.01–0.02 mg/kg intramuscularly. Treatment with oral doses of these agents should be continued for 24–48 hours.

Bromocriptine (2.5–7.5 mg orally daily) may be effective for mild or moderate neuroleptic malignant syndrome. Dantrolene (2–5 mg/kg intravenously) has also been used for muscle rigidity but is not a true antidote. For severe hyperthermia, rapid neuromuscular paralysis is preferred.

Beach SR et al. QT prolongation, torsades de pointes, and psychotropic medications: a 5-year update. *Psychosomatics*. 2018;59:105. [PMID: 29275963]

Christensen AP et al. Overdoses with aripiprazole: signs, symptoms and outcome in 239 exposures reported to the Danish Poison Information Centre. *Basic Clin Pharmacol Toxicol*. 2018;122:293. [PMID: 28881461]

Peridy E et al. Quetiapine poisoning and factors influencing severity. *J Clin Psychopharmacol*. 2019;39:312. [PMID: 31205192]

ARSENIC

Arsenic is found in some pesticides and industrial chemicals and is used as a chemotherapeutic agent. Chronic arsenic poisoning has been associated with contaminated aquifers used for drinking water. Symptoms of acute poisoning usually appear within 1 hour after ingestion but

may be delayed as long as 12 hours. They include abdominal pain, vomiting, watery diarrhea, and skeletal muscle cramps. Profound dehydration and shock may occur. In chronic poisoning, symptoms can be vague but often include pancytopenia, painful peripheral sensory neuropathy, and skin changes including melanosis, keratosis, and desquamating rash. Cancers of the lung, bladder, and skin have been reported. Urinary arsenic levels may be falsely elevated after certain meals (eg, seafood) that contain large quantities of a nontoxic form of organic arsenic.

► Treatment

A. Emergency Measures

After recent ingestion (within 1–2 hours), perform gastric lavage. Activated charcoal is of uncertain benefit because it binds arsenic poorly. Administer intravenous fluids to replace losses due to vomiting and diarrhea.

B. Antidote

For patients with severe acute intoxication, administer a chelating agent. The preferred drug is 2,3-dimercaptopropanesulfonic acid (DMPS, Unithiol) (3–5 mg/kg intravenously every 4 hours); although there is no FDA-approved commercial formulation of DMPS in the United States, it can be obtained from some compounding pharmacies. An alternative parenteral chelator is dimercaprol (British anti-Lewisite, BAL), which comes as a 10% solution in peanut oil and is given as 3–5 mg/kg intramuscularly every 4–6 hours for 2 days. The side effects include nausea, vomiting, headache, and hypertension. When gastrointestinal symptoms allow, switch to the oral chelator succimer (dimercaptosuccinic acid, DMSA), 10 mg/kg every 8 hours, for 1 week. Consult a medical toxicologist or regional poison control center (1-800-222-1222) for advice regarding chelation.

Bjorklund G et al. Arsenic intoxication: general aspects and chelating agents. *Arch Toxicol*. 2020;94:1879. [PMID: 32388818]
Dani SU et al. Chronic arsenic intoxication diagnostic score (CAsIDS). *J Appl Toxicol*. 2018;38:122. [PMID: 28857213]

ATROPINE & ANTICHOLINERGICS

Atropine, scopolamine, belladonna, *Datura stramonium*, *Hyoscyamus niger*, some mushrooms, tricyclic antidepressants, and antihistamines are antimuscarinic agents with variable central nervous system effects. Symptoms of toxicity include dryness of the mouth, thirst, difficulty in swallowing, and blurring of vision. Physical signs include dilated pupils, flushed skin, tachycardia, fever, delirium, myoclonus, and ileus. Antidepressants and antihistamines may also induce convulsions.

Antihistamines are commonly available with or without prescription. Diphenhydramine commonly causes delirium, tachycardia, and seizures. Massive diphenhydramine overdose may mimic tricyclic antidepressant cardiotoxic poisoning.

► Treatment

A. Emergency and Supportive Measures

Administer activated charcoal. External cooling and sedation, or neuromuscular paralysis in rare cases, are indicated to control high temperatures.

B. Specific Treatment

For severe anticholinergic syndrome (eg, agitated delirium), give physostigmine salicylate, 0.5–1 mg slowly intravenously over 5 minutes, with ECG monitoring; repeat as needed to a total dose of no more than 2 mg. **Caution:** Bradyarrhythmias and convulsions are a hazard with physostigmine administration, and the drug should be avoided in patients with evidence of cardiotoxic effects (eg, QRS interval prolongation) from tricyclic antidepressants or other sodium channel blockers.

Arens AM et al. Adverse effects of physostigmine. *J Med Toxicol*. 2019;15:184. [PMID: 30747326]

Chung WM et al. *Datura* fruit poisoning. *Med J Malaysia*. 2018;73:453. [PMID: 30647232]

Jayawickreme KP et al. Unknowing ingestion of *Brugmansia suaveolens* leaves presenting with signs of anticholinergic toxicity: a case report. *J Med Case Rep*. 2019;13:322. [PMID: 31665073]

BETA-ADRENERGIC BLOCKERS

There are a wide variety of beta-adrenergic blocking drugs, with varying pharmacologic and pharmacokinetic properties (see Table 11–9). The most toxic beta-blocker is propranolol, which not only blocks beta-1- and beta-2-adrenoceptors but also has direct membrane-depressant and central nervous system effects.

► Clinical Findings

The most common findings with mild or moderate intoxication are hypotension and bradycardia. Cardiac depression from more severe poisoning is often unresponsive to conventional therapy with beta-adrenergic stimulants such as dopamine and norepinephrine. In addition, with propranolol and other lipid-soluble drugs, seizures and coma may occur. Propranolol, oxprenolol, acebutolol, and alprenolol also have membrane-depressant effects and can cause conduction disturbance (wide QRS interval) similar to tricyclic antidepressant overdose.

The diagnosis is based on typical clinical findings. Routine toxicology screening does not usually include beta-blockers.

► Treatment

A. Emergency and Supportive Measures

Attempts to treat bradycardia or heart block with atropine (0.5–2 mg intravenously), isoproterenol (2–20 mcg/min by intravenous infusion, titrated to the desired heart rate), or an external transcutaneous cardiac pacemaker are often ineffective, and specific antidotal treatment may be necessary.

For drugs ingested within an hour of presentation (or longer after ingestion of an extended-release formulation), administer activated charcoal.

B. Specific Treatment

For persistent bradycardia and hypotension, give glucagon, 5–10 mg intravenously, followed by an infusion of 1–5 mg/h. Glucagon is an inotropic agent that acts at a different receptor site and is therefore not affected by beta-blockade. High-dose insulin (0.5–1 unit/kg/h intravenously) along with glucose supplementation has also been used to reverse severe cardiotoxicity. Membrane-depressant effects (wide QRS interval) may respond to boluses of sodium bicarbonate (50–100 mEq intravenously) as for tricyclic antidepressant poisoning. Intravenous lipid emulsion (Intralipid 20%, 1.5 mL/kg) has been used successfully in severe propranolol overdose. ECMO should be considered for refractory shock.

Krenz JR et al. An overview of hyperinsulinemic-euglycemic therapy in calcium channel blocker and β -blocker overdose. *Pharmacotherapy*. 2018;38:1130. [PMID: 30141827]
Rotella JA et al. Treatment for beta-blocker poisoning: a systematic review. *Clin Toxicol (Phila)*. 2020;58:943. [PMID: 32310006]

CALCIUM CHANNEL BLOCKERS

In therapeutic doses, nifedipine, nicardipine, amlodipine, felodipine, isradipine, nisoldipine, and nimodipine act mainly on blood vessels, while verapamil and diltiazem act mainly on cardiac contractility and conduction. However, these selective effects can be lost after acute overdose. Patients may present with bradycardia, atrioventricular (AV) nodal block, hypotension, or a combination of these effects. Hyperglycemia is common due to blockade of insulin release. With severe poisoning, cardiac arrest may occur.

Treatment

A. Emergency and Supportive Measures

For ingested drugs, administer activated charcoal. In addition, whole bowel irrigation should be initiated as soon as possible if the patient has ingested a sustained-release product.

B. Specific Treatment

Treat symptomatic bradycardia with atropine (0.5–2 mg intravenously), isoproterenol (2–20 mcg/min by intravenous infusion), or a transcutaneous cardiac pacemaker. For hypotension, give calcium chloride 10%, 10 mL, or calcium gluconate 10%, 20 mL. Repeat the dose every 3–5 minutes. The optimum (or maximum) dose has not been established, but many toxicologists recommend raising the ionized serum calcium level to as much as twice the normal level. Calcium is most useful in reversing negative inotropic effects and is less effective for AV nodal blockade and bradycardia. High doses of insulin (0.5–1 unit/kg intravenous bolus followed by 0.5–1 unit/kg/h infusion) along with sufficient dextrose to maintain euglycemia have been

reported to be beneficial, but there are no controlled studies. Infusion of Intralipid 20% lipid emulsion has been reported to improve hemodynamics in animal models and case reports of calcium channel blocker poisoning. Methylene blue (1–2 mg/kg) was reported to reverse refractory shock due to profound vasodilation in a patient with amiodipine poisoning. ECMO has been recommended for refractory shock.

Ramanathan K et al. Extracorporeal therapy for amlodipine poisoning. *J Artif Organs*. 2020;23:183. [PMID: 31552515]
Seegobin K et al. Severe beta blocker and calcium channel blocker overdose: role of high dose insulin. *Am J Emerg Med*. 2018;36:736.e5. [PMID: 29331270]

CARBON MONOXIDE

Carbon monoxide is a colorless, odorless gas produced by the combustion of carbon-containing materials. Poisoning may occur as a result of suicidal or accidental exposure to automobile exhaust, smoke inhalation in a fire, or accidental exposure to an improperly vented gas heater, generator, or other appliance. Carbon monoxide can be generated during degradation of some anesthetic gases by carbon dioxide adsorbents. Carbon monoxide avidly binds to hemoglobin, with an affinity approximately 250 times that of oxygen. This results in reduced oxygen-carrying capacity and altered delivery of oxygen to cells (see also Smoke Inhalation in Chapter 9).

Clinical Findings

At low carbon monoxide levels (carboxyhemoglobin saturation 10–20%), victims may have headache, dizziness, abdominal pain, and nausea. With higher levels, confusion, dyspnea, and syncope may occur. Hypotension, coma, and seizures are common with levels greater than 50–60%. Survivors of acute severe poisoning may develop permanent obvious or subtle neurologic and neuropsychiatric deficits. The fetus and newborn may be more susceptible because of high carbon monoxide affinity for fetal hemoglobin.

Carbon monoxide poisoning should be suspected in any person with severe headache or acutely altered mental status, especially during cold weather, when improperly vented heating systems may have been used. Diagnosis depends on specific measurement of the arterial or venous carboxyhemoglobin saturation, although the level may have declined if high-flow oxygen therapy has already been administered, and levels do not always correlate with clinical symptoms. Routine arterial blood gas testing and pulse oximetry are *not* useful because they give falsely normal PaO₂ and oxyhemoglobin saturation determinations, respectively. (A specialized pulse oximetry device, the Masimo pulse CO-oximeter, is capable of distinguishing oxyhemoglobin from carboxyhemoglobin.)

Treatment

A. Emergency and Supportive Measures

Maintain a patent airway and assist ventilation, if necessary. Remove the victim from exposure. Treat patients with

coma, hypotension, or seizures as described at the beginning of this chapter.

B. Specific Treatment

The half-life of the carboxyhemoglobin (CoHb) complex is about 4–5 hours in room air but is reduced dramatically by high concentrations of oxygen. Administer 100% oxygen by tight-fitting high-flow reservoir face mask or endotracheal tube. **Hyperbaric oxygen (HBO)** can provide 100% oxygen under higher than atmospheric pressures, further shortening the half-life; it may also reduce the incidence of subtle neuropsychiatric sequelae. Randomized controlled studies disagree about the benefit of HBO, but commonly recommended indications for HBO in patients with carbon monoxide poisoning include a history of loss of consciousness, CoHb greater than 25%, metabolic acidosis, age over 50 years, and cerebellar findings on neurologic examination.

Casillas S et al. Effectiveness of hyperbaric oxygenation versus normobaric oxygenation therapy in carbon monoxide poisoning: a systematic review. *Cureus*. 2019;11:e5916. [PMID: 31788375]

Lin CH et al. Treatment with normobaric or hyperbaric oxygen and its effect on neuropsychometric dysfunction after carbon monoxide poisoning: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2018;97:e12456. [PMID: 30278526]

Agency for Toxic Substances and Disease Registry. Toxic Substances Portal. 2021 Feb 9. <https://www.atsdr.cdc.gov/>

Hulse EJ et al. Organophosphorus nerve agent poisoning: managing the poisoned patient. *Br J Anaesth*. 2019;123:457. [PMID: 31248646]

Richardson JR et al. Neurotoxicity of pesticides. *Acta Neuropathol*. 2019;138:343. [PMID: 31197504]

Timperley CM et al. Advice on assistance and protection from the Scientific Advisory Board of the Organisation for the Prohibition of Chemical Weapons: Part 2. On preventing and treating health effects from acute, prolonged, and repeated nerve agent exposure, and the identification of medical countermeasures able to reduce or eliminate the longer-term health effects of nerve agents. *Toxicology*. 2019;413:13. [PMID: 30500381]

United States Department of Labor. Occupational Safety and Health Administration. Safety and Health Guides/Nerve Agents Guide. <https://www.osha.gov/SLTC/emergency-preparedness/guides/nerve.html>

CLONIDINE & OTHER SYMPATHOLYTIC ANTIHYPERTENSIVES

Overdosage with these agents (clonidine, guanabenz, guanfacine, methyldopa) causes bradycardia, hypotension, miosis, respiratory depression, and coma. (Transient hypertension occasionally occurs after acute overdosage, a result of peripheral alpha-adrenergic effects in high doses.) Symptoms are usually resolved in less than 24 hours, and deaths are rare. Similar symptoms may occur after ingestion of topical nasal decongestants chemically similar to clonidine (oxymetazoline, tetrahydrozoline, naphazoline). Brimonidine and apraclonidine are used as ophthalmic preparations for glaucoma. Tizanidine is a centrally acting muscle relaxant structurally related to clonidine; it produces similar toxicity in overdose.

Treatment

A. Emergency and Supportive Measures

Give activated charcoal. Maintain the airway and support respiration if necessary. Symptomatic treatment is usually sufficient even in massive overdose. Maintain blood pressure with intravenous fluids. Dopamine can also be used. Atropine is usually effective for bradycardia.

B. Specific Treatment

There is no specific antidote. Naloxone has been reported to be successful in a few anecdotal cases and retrospective studies.

Toce MS et al. Clinical effects of pediatric clonidine exposure: a retrospective cohort study at a single tertiary care center. *J Emerg Med*. 2021;60:58. [PMID: 33036823]

COCAINE

See Amphetamines & Cocaine.

CYANIDE

Cyanide is a highly toxic chemical used widely in research and commercial laboratories and many industries. Its gaseous form, hydrogen cyanide, is an important component

CHEMICAL WARFARE: NERVE AGENTS

Nerve agents used in chemical warfare work by cholinesterase inhibition and are most commonly organophosphorus compounds. Agents such as **tabun** (GA), **sarin** (GB), **soman** (GD), and **VX** are similar to insecticides such as malathion but are vastly more potent. They may be inhaled or absorbed through the skin. Systemic effects due to unopposed action of acetylcholine include miosis, salivation, abdominal cramps, diarrhea, and muscle paralysis producing respiratory arrest. Inhalation also produces severe bronchoconstriction and copious nasal and tracheobronchial secretions.

Treatment

A. Emergency and Supportive Measures

Perform thorough decontamination of exposed areas with repeated soap and shampoo washing. Personnel caring for such patients must wear protective clothing and gloves, since cutaneous absorption may occur through normal skin.

B. Specific Treatment

Give atropine in an initial dose of 2 mg intravenously and repeat as needed to reverse signs of acetylcholine excess. (Some victims have required several hundred milligrams.) Treat also with the cholinesterase-reactivating agent pralidoxime, 1–2 g intravenously initially followed by an infusion at a rate of 200–400 mg/h.

of smoke in fires. Cyanide-generating glycosides are also found in the pits of apricots and other related plants. Cyanide is generated by the breakdown of nitroprusside, and poisoning can result from rapid high-dose infusions. Cyanide is also formed by metabolism of acetonitrile, a solvent found in some over-the-counter fingernail glue removers. Cyanide is rapidly absorbed by inhalation, skin absorption, or ingestion. It disrupts cellular function by inhibiting cytochrome oxidase and preventing cellular oxygen utilization.

► Clinical Findings

The onset of toxicity is nearly instantaneous after inhalation of hydrogen cyanide gas but may be delayed for minutes to hours after ingestion of cyanide salts or cyanogenic plants or chemicals. Effects include headache, dizziness, nausea, abdominal pain, and anxiety, followed by confusion, syncope, shock, seizures, coma, and death. The odor of “bitter almonds” may be detected on the victim’s breath or in vomitus, though this is not a reliable finding. The venous oxygen saturation may be elevated (greater than 90%) in severe poisonings because tissues have failed to take up arterial oxygen.

► Treatment

A. Emergency and Supportive Measures

Remove the victim from exposure, taking care to avoid exposure to rescuers. For suspected cyanide poisoning due to nitroprusside infusion, stop or slow the rate of infusion. (Metabolic acidosis and other signs of cyanide poisoning usually clear rapidly.)

For cyanide ingestion, administer activated charcoal. Although charcoal has a low affinity for cyanide, the usual doses of 60–100 g are adequate to bind typically ingested lethal doses (100–200 mg).

B. Specific Treatment

In the United States, there are two available cyanide antidote regimens. The conventional cyanide antidote package (Nithiodote) contains sodium nitrite (to induce methemoglobinemia, which binds free cyanide) and sodium thiosulfate (to promote conversion of cyanide to the less toxic thiocyanate). Administer 3% sodium nitrite solution, 10 mL intravenously, followed by 25% sodium thiosulfate solution, 50 mL intravenously (12.5 g). **Caution:** Nitrites may induce hypotension and dangerous levels of methemoglobin.

The other approved cyanide treatment in the United States is hydroxocobalamin (Cyanokit, EMD Pharmaceuticals), a newer and potentially safer antidote. The adult dose of hydroxocobalamin is 5 g intravenously (children’s dose is 70 mg/kg). **Note:** Hydroxocobalamin causes red discoloration of skin and body fluids that may last several days and can interfere with some laboratory tests.

DIETARY SUPPLEMENTS & HERBAL PRODUCTS

Unlike prescription and over-the-counter pharmaceuticals, dietary supplements do not require FDA approval and do not undergo the same premarketing evaluation of safety and efficacy as drugs, and purveyors may or may not adhere to good manufacturing practices and quality control standards. Supplements may cause illness as a result of intrinsic toxicity, misidentification or mislabeling, drug-herb reactions, or intentional adulteration with pharmaceuticals. If you suspect a dietary supplement or herbal product may be the cause of an otherwise unexplained illness, contact the FDA (1-888-463-6332) or the regional poison control center (1-800-222-1222), or consult the following online database: <https://www.fda.gov/food/dietary-supplements>.

Table 38-7 lists selected examples of clinical toxicity from some of these products.

Charen E et al. Toxicity of herbs, vitamins and supplements. *Adv Chronic Kidney Dis.* 2020;27:67. [PMID: 32147004]

Lim DY et al. Collective exposure to lead from an approved natural product-derived drug in Korea. *Ann Occup Environ Med.* 2019;31:e20. [PMID: 31620297]

DIGITALIS & OTHER CARDIAC GLYCOSIDES

Cardiac glycosides paralyze the Na⁺-K⁺-ATPase pump and have potent vagotonic effects. Intracellular effects include enhancement of calcium-dependent contractility and shortening of the action potential duration. A number of plants (eg, oleander, foxglove, lily-of-the-valley) contain cardiac glycosides. Bufotenin, a cardiotoxic steroid found in certain toad secretions and used as an herbal medicine and a purported aphrodisiac, has pharmacologic properties similar to cardiac glycosides.

► Clinical Findings

Intoxication may result from acute single exposure or chronic accidental overmedication, especially in patients with kidney dysfunction taking digoxin. After acute overdosage, nausea and vomiting, bradycardia, hyperkalemia, and AV block frequently occur. Patients in whom toxicity develops gradually during long-term therapy may be hypokalemic and hypomagnesemic owing to concurrent diuretic treatment and more commonly present with ventricular arrhythmias (eg, ectopy, bidirectional ventricular tachycardia, or ventricular fibrillation). Digoxin levels may be only slightly elevated in patients with intoxication from cardiac glycosides other than digoxin because of limited cross-reactivity of immunologic tests.

► Treatment

A. Emergency and Supportive Measures

After acute ingestion, administer activated charcoal. Monitor potassium levels and cardiac rhythm closely. Treat bradycardia initially with atropine (0.5–2 mg intravenously) or a transcutaneous external cardiac pacemaker.

- Hendry-Hofer TB et al. A review on ingested cyanide: risks, clinical presentation, diagnostics, and treatment challenges. *J Med Toxicol.* 2019;15:128. [PMID: 30539383]
 Parker-Cote JL et al. Challenges in the diagnosis of acute cyanide poisoning. *Clin Toxicol (Phila).* 2018;56:609. [PMID: 29417853]

Table 38–7. Examples of potential toxicity associated with some dietary supplements and herbal medicines (listed in alphabetical order).

Product	Common Use	Possible Toxicity
Azarcon (Greta)	Mexican folk remedy for abdominal pain, colic	Contains lead
Comfrey	Gastric upset, diarrhea	Contains pyrrolizidine alkaloids, can cause hepatic veno-occlusive disease
Creatine	Athletic performance enhancement	Nausea, diarrhea, abdominal cramps; elevated serum creatinine
Ginkgo	Memory improvement, tinnitus	Antiplatelet effects, hemorrhage; abdominal pain, diarrhea
Ginseng	Immune system; stress	Decreased glucose; increased cortisol
Guarana	Athletic performance enhancement, appetite suppression	Contains caffeine: can cause tremor, tachycardia, vomiting
Kava	Anxiety, insomnia	Drowsiness, hepatitis, skin rash
Ma huang	Stimulant; athletic performance enhancement	Contains ephedrine: anxiety, insomnia, hypertension, tachycardia, seizures
Spirulina	Body building	Niacin-like flushing reaction
Yohimbine	Sexual enhancement	Hallucinations, hypertension, tachycardia
Zinc	Cold/flu symptoms	Nausea, oral irritation, anosmia

Adapted, with permission, from Table II-30 by Haller C in "Herbal and Alternative Products," In: Olson KR (ed.) *Poisoning & Drug Overdose*, 7th edition. McGraw-Hill, 2018.

B. Specific Treatment

For patients with significant intoxication, administer digoxin-specific antibodies (digoxin immune Fab [ovine]; DigiFab). Estimation of the dose is based on the body burden of digoxin calculated from the ingested dose or the steady-state serum digoxin concentration, as described below. More effective binding of digoxin may be achieved if the dose is given partly as a bolus and the remainder as an infusion over a few hours.

Arbabian H et al. Elderly patients with suspected chronic digoxin toxicity: a comparison of clinical characteristics of patients receiving and not receiving digoxin-Fab. *Emerg Med Australas.* 2018;30:242. [PMID: 29316267]

Cham BS et al. Clinical outcomes from early use of digoxin-specific antibodies versus observation in chronic digoxin poisoning (ATOM-4). *Clin Toxicol (Phila).* 2019;57:638. [PMID: 30585517]

ETHANOL, BENZODIAZEPINES, & OTHER SEDATIVE-HYPNOTIC AGENTS

The group of agents known as sedative-hypnotic drugs includes a variety of products used for the treatment of anxiety, depression, insomnia, and epilepsy. Besides common benzodiazepines, such as lorazepam, alprazolam, clonazepam, diazepam, oxazepam, chlordiazepoxide, and triazolam, this group includes the newer benzodiazepine-like hypnotics zolpidem, zopiclone, and zaleplon, the muscle relaxants baclofen and carisoprodol, and barbiturates such as phenobarbital. Ethanol and other selected agents are also popular recreational drugs. All of these drugs depress the central nervous system reticular activating system, cerebral cortex, and cerebellum.

► Clinical Findings

Mild intoxication produces euphoria, slurred speech, and ataxia. Ethanol intoxication may produce hypoglycemia, even at relatively low concentrations, in children and in fasting adults. With more severe intoxication, stupor, coma, and respiratory arrest may occur. Carisoprodol (Soma) commonly causes muscle jerking or myoclonus.

1. From the ingested dose—Number of vials = approximately 1.5–2 × ingested dose (mg).

2. From the serum concentration—Number of vials = serum digoxin (ng/mL) × body weight (kg) × 10⁻². **Note:** This is based on the equilibrium digoxin level; after acute overdose, serum levels may be falsely high for several hours before tissue distribution is complete, and overestimation of the DigiFab dose is likely.

3. Empiric dosing—Empiric titration of DigiFab may be used if the patient's condition is relatively stable and an underlying condition (eg, atrial fibrillation) favors retaining a residual level of digitalis activity. Start with one or two vials and reassess the patient's clinical condition after 20–30 minutes. For cardiac glycosides other than digoxin or digitoxin, there is no formula for estimation of vials needed and treatment is entirely based on response to empiric dosing.

Note: After administration of digoxin-specific Fab antibody fragments, serum digoxin levels may be falsely elevated depending on the assay technique.

Death or serious morbidity is usually the result of pulmonary aspiration of gastric contents. Bradycardia, hypotension, and hypothermia are common. Patients with massive intoxication may appear to be dead, with no reflex responses and even absent electroencephalographic activity. Diagnosis and assessment of severity of intoxication are usually based on clinical findings. Ethanol serum levels over 300 mg/dL (0.3 g/dL; 65 mmol/L) can produce coma in infrequent drinkers, while regular drinkers may remain awake at much higher levels.

► Treatment

A. Emergency and Supportive Measures

Administer activated charcoal if the patient has ingested a massive dose and the airway is protected. Repeat-dose charcoal may enhance elimination of phenobarbital, but it has not been proved to improve clinical outcome. Hemodialysis may be necessary for patients with severe phenobarbital intoxication.

B. Specific Treatment

Flumazenil is a benzodiazepine receptor-specific antagonist; it has no effect on ethanol, barbiturates, or other sedative-hypnotic agents. If used, flumazenil is given slowly intravenously, 0.2 mg over 30–60 seconds, and repeated in 0.2–0.5 mg increments as needed up to a total dose of 3–5 mg. **Caution:** Flumazenil should rarely be used because it may induce seizures in patients with preexisting seizure disorder, benzodiazepine tolerance, or concomitant tricyclic antidepressant or other convulsant overdose. If seizures occur, diazepam and other benzodiazepine anticonvulsants may not be effective. As with naloxone, the duration of action of flumazenil is short (2–3 hours) and resedation may occur, requiring repeated doses.

Krause M et al. Toxin-induced coma and central nervous system depression. *Neurol Clin.* 2020;38:825. [PMID: 33040863]

GAMMA-HYDROXYBUTYRATE (GHB)

GHB is a popular drug of abuse. It originated as a short-acting general anesthetic and is occasionally used in the treatment of narcolepsy. It gained popularity among body-builders for its alleged growth hormone stimulation and found its way into social settings, where it is consumed as a liquid. It has been used to facilitate sexual assault (“**date-rape**” drug). Symptoms after ingestion include drowsiness and lethargy followed by coma with respiratory depression. Muscle twitching and seizures are sometimes observed. Recovery is usually rapid, with patients awakening within a few hours. Other related chemicals with similar effects include butanediol and gamma-butyrolactone (GBL). A prolonged withdrawal syndrome has been described in some heavy users.

► Treatment

Monitor the airway and assist breathing if needed. There is no specific treatment. Most patients recover rapidly with

supportive care. GHB withdrawal syndrome may require very large doses of benzodiazepines; baclofen has also been used.

Busardò FP et al. Interpreting γ -hydroxybutyrate concentrations for clinical and forensic purposes. *Clin Toxicol (Phila).* 2019;57:149. [PMID: 30307336]

Marinelli E et al. Gamma-hydroxybutyrate abuse: pharmacology and poisoning and withdrawal management. *Arh Hig Rada Toksikol.* 2020;71:19. [PMID: 32597141]

HYPOGLYCEMIC DRUGS

Medications used for diabetes mellitus include insulin, sulfonylureas and other insulin secretagogues, alpha-glucosidase inhibitors (acarbose, miglitol), biguanides (metformin), thiazolidinediones (pioglitazone, rosiglitazone), sodium glucose transporter (SGLT2) inhibitors, and peptide analogs (pramlintide, exenatide) or enhancers (sitagliptin) (see Chapter 27). Of these, insulin and the insulin secretagogues are the most likely to cause hypoglycemia. Metformin can cause lactic acidosis, especially in patients with impaired kidney function or after intentional drug overdose. Euglycemic diabetic ketoacidosis has been reported with SGLT2 use. Table 27–5 lists the duration of hypoglycemic effect of oral hypoglycemic agents and Table 27–6 the extent and duration of various types of insulins.

► Clinical Findings

Hypoglycemia may occur quickly after injection of short-acting insulins or may be delayed and prolonged, especially if a large amount has been injected into a single area, creating a “depot” effect. Hypoglycemia after sulfonylurea ingestion is usually apparent within a few hours but may be delayed several hours, especially if food or glucose-containing fluids have been given.

► Treatment

Give sugar and carbohydrate-containing food or liquids by mouth, or intravenous dextrose if the patient is unable to swallow safely. For severe hypoglycemia, start with D50W, 50 mL intravenously (25 g dextrose); repeat, if needed. Follow up with dextrose-containing intravenous fluids (D5W or D10W) to maintain a blood glucose greater than 70–80 mg/dL.

For hypoglycemia caused by sulfonylureas and related insulin secretagogues, consider use of octreotide, a synthetic somatostatin analog that blocks pancreatic insulin release. A dose of 50–100 mcg octreotide subcutaneously every 6–12 hours can reduce the need for exogenous dextrose and prevent rebound hypoglycemia from excessive dextrose dosing.

Admit all patients with symptomatic hypoglycemia after sulfonylurea overdose. Observe asymptomatic overdose patients for at least 12 hours.

Consider hemodialysis for patients with metformin overdose accompanied by severe lactic acidosis (lactate greater than 20 mmol/L or pH < 7.0).

Razavi-Nematollahi L et al. Adverse effects of glycemia-lowering medications in type 2 diabetes. *Curr Diab Rep.* 2019;19:132. [PMID: 31748838]

Schein AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. *Circ Res.* 2018;122:1439. [PMID: 29748368]

Ueda P et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register-based cohort study. *BMJ.* 2018;363:k4365. [PMID: 30429124]

ISONIAZID

Isoniazid (INH) is an antibiotic used mainly in the treatment and prevention of tuberculosis. It may cause hepatitis with long-term use, especially in alcoholic patients and elderly persons. It produces acute toxic effects by competing with pyridoxal 5-phosphate, resulting in lowered brain gamma-aminobutyric acid (GABA) levels. Acute ingestion of as little as 1.5–2 g of INH can cause toxicity, and severe poisoning is likely to occur after ingestion of more than 80–100 mg/kg.

► Clinical Findings

Confusion, slurred speech, and seizures may occur abruptly after acute overdose. Severe lactic acidosis—out of proportion to the severity of seizures—is probably due to inhibited metabolism of lactate. Peripheral neuropathy and acute hepatitis may occur with long-term use.

Diagnosis is based on a history of ingestion and the presence of severe acidosis associated with seizures. INH is not usually included in routine toxicologic screening, and serum levels are not readily available.

► Treatment

A. Emergency and Supportive Measures

Seizures may require higher than usual doses of benzodiazepines (eg, lorazepam, 3–5 mg intravenously) or administration of pyridoxine as an antidote.

Administer activated charcoal after large recent ingestion, but with caution because of the risk of abrupt onset of seizures.

B. Specific Treatment

Pyridoxine (vitamin B₆) is a specific antagonist of the acute toxic effects of INH and is usually successful in controlling convulsions that do not respond to benzodiazepines. Give 5 g intravenously over 1–2 minutes or, if the amount ingested is known, give a gram-for-gram equivalent amount of pyridoxine. Patients taking INH are usually given 25–50 mg of pyridoxine orally daily to help prevent neuropathy.

Glatstein M et al. Pyridoxine for the treatment of isoniazid-induced seizures in intentional ingestions: the experience of a national poison center. *Am J Emerg Med.* 2018;36:1775. [PMID: 29397257]

LEAD

Lead is used in a variety of industrial and commercial products, such as firearms ammunition, storage batteries, solders, paints, pottery, plumbing, and gasoline and is

found in some traditional Hispanic and Ayurvedic ethnic medicines. *Lead toxicity usually results from chronic repeated exposure and is rare after a single ingestion.* Lead produces a variety of adverse effects on cellular function and primarily affects the nervous system, gastrointestinal tract, and hematopoietic system.

► Clinical Findings

Lead poisoning often goes undiagnosed initially because presenting symptoms and signs are nonspecific and exposure is not suspected. Common symptoms include colicky abdominal pain, constipation, headache, and irritability. Severe poisoning may cause coma and convulsions. Chronic intoxication can cause learning disorders (in children) and motor neuropathy (eg, wrist drop). Lead-containing bullet fragments in or near joint spaces can result in chronic lead toxicity.

Diagnosis is based on measurement of the blood lead level. Whole blood lead levels above 5 mcg/dL warrant public health investigation. Levels between 10 and 25 mcg/dL have been associated with impaired neurobehavioral development in children. Levels of 25–50 mcg/dL may be associated with headache, irritability, and subclinical neuropathy. Levels of 50–70 mcg/dL are associated with moderate toxicity, and levels greater than 70–100 mcg/dL are often associated with severe poisoning. Other laboratory findings of lead poisoning include microcytic anemia with basophilic stippling and elevated free erythrocyte protoporphyrin.

► Treatment

A. Emergency and Supportive Measures

The most critical intervention in the treatment of lead poisoning is identification of and removal from the source of exposure. For patients with encephalopathy, maintain a patent airway and treat coma and convulsions as described at the beginning of this chapter.

For recent acute ingestion, if a large lead-containing object (eg, fishing weight) is still visible in the stomach on abdominal radiograph, whole bowel irrigation, endoscopy, or even surgical removal may be necessary to prevent subacute lead poisoning. (The acidic gastric contents may corrode the metal surface, enhancing lead absorption. Once the object passes into the small intestine, the risk of toxicity declines.)

B. Specific Treatment

The indications for chelation depend on the blood lead level and the patient's clinical state. A medical toxicologist or regional poison control center (1-800-222-1222) should be consulted for advice about selection and use of these antidotes.

1. Severe toxicity—Patients with severe intoxication (encephalopathy or levels greater than 70–100 mcg/dL) should receive edetate calcium disodium (ethylenediaminetetraacetic acid, EDTA), 1500 mg/m²/kg/day (approximately 50 mg/kg/day) in four to six divided doses or as a continuous intravenous infusion. Most clinicians also add

dimercaprol (BAL), 4–5 mg/kg intramuscularly every 4 hours for 5 days, for patients with encephalopathy.

2. Less severe toxicity—Patients with less severe symptoms and asymptomatic patients with blood lead levels between 55 and 69 mcg/dL may be treated with edetate calcium disodium alone in dosages as above. An oral chelator, succimer (DMSA), is available for use in patients with mild to moderate intoxication. The usual dose is 10 mg/kg orally every 8 hours for 5 days, then every 12 hours for 2 weeks.

Angelon-Gaetz KA et al. Lead in spices, herbal remedies, and ceremonial powders sampled from home investigations for children with elevated blood lead levels—North Carolina, 2011–2018. MMWR Morb Mortal Wkly Rep. 2018;67:1290. [PMID: 30462630]

Reuben A. Childhood lead exposure and adult neurodegenerative disease. J Alzheimers Dis. 2018;64:17. [PMID: 29865081]

LITHIUM

Lithium is widely used for the treatment of bipolar depression and other psychiatric disorders. The only normal route of lithium elimination is via the kidney, so patients with acute or chronic kidney disorders are at risk for accumulation of lithium resulting in gradual onset (chronic) toxicity. Intoxication resulting from chronic accidental overmedication or kidney impairment is more common and usually more severe than that seen after acute oral overdose.

Clinical Findings

Mild to moderate toxicity causes lethargy, confusion, tremor, ataxia, and slurred speech. This may progress to myoclonic jerking, delirium, coma, and convulsions. Recovery may be slow and incomplete following severe intoxication. Laboratory studies in patients with chronic intoxication often reveal an elevated serum creatinine and an elevated BUN/creatinine ratio due to underlying volume contraction. The white blood cell count is often elevated. ECG findings include T-wave flattening or inversion, and sometimes bradycardia or sinus node arrest. Nephrogenic diabetes insipidus can occur with overdose or with therapeutic doses. Dysfunction of the thyroid and parathyroid glands has also been described as a result of prolonged lithium exposure.

Lithium levels may be difficult to interpret. Lithium has a low toxic:therapeutic ratio, and chronic intoxication can be seen with levels only slightly above the therapeutic range (0.8–1.2 mEq/L). In contrast, patients with acute ingestion may have transiently very high levels (up to 10 mEq/L reported) without any symptoms before the lithium fully distributes into tissues. **Note:** Falsely high lithium levels (as high as 6–8 mEq/L) can be measured if a green-top blood specimen tube (containing lithium heparin) is used for blood collection.

Treatment

After acute oral overdose, consider gastric lavage or whole bowel irrigation to prevent systemic absorption (**Note:** lithium is *not* adsorbed by activated charcoal). In all

patients, evaluate kidney function and volume status, and give intravenous saline-containing fluids as needed. Monitor serum lithium levels and seek assistance with their interpretation and the need for dialysis from a medical toxicologist or regional poison control center (1-800-222-1222). Consider hemodialysis if the patient is markedly symptomatic or if the serum lithium level exceeds 4–5 mEq/L, especially if kidney function is impaired. Continuous renal replacement therapy may be an effective alternative to hemodialysis.

Hlaing PM et al. Neurotoxicity in chronic lithium poisoning. Intern Med J. 2020;50:427. [PMID: 31211493]

King JD et al. Extracorporeal removal of poisons and toxins. Clin J Am Soc Nephrol. 2019;14:1408. [PMID: 31439539]

LSD & OTHER HALLUCINOGENS

A variety of substances—ranging from naturally occurring plants and mushrooms to synthetic substances such as phencyclidine (PCP), toluene and other solvents, dextromethorphan, and lysergic acid diethylamide (LSD)—are abused for their hallucinogenic properties. The mechanism of toxicity and the clinical effects vary for each substance.

Many hallucinogenic plants and mushrooms produce anticholinergic delirium, characterized by flushed skin, dry mucous membranes, dilated pupils, tachycardia, and urinary retention. Other plants and mushrooms may contain hallucinogenic indoles such as mescaline and LSD, which typically cause marked visual hallucinations and perceptual distortion, widely dilated pupils, and mild tachycardia. PCP, a dissociative anesthetic agent similar to ketamine, can produce fluctuating delirium and coma, often associated with vertical and horizontal nystagmus. Toluene and other hydrocarbon solvents (butane, trichloroethylene, “chemo,” etc) cause euphoria and delirium and may sensitize the myocardium to the effects of catecholamines, leading to fatal dysrhythmias. Other drugs used for their psychostimulant effects include synthetic cannabinoid receptor agonists, *Salvia divinorum*, synthetic tryptamines, and phenylethylamines, and mephedrone and related cathinone derivatives. See <https://www.erowid.org/psychoactives/psychoactives.shtml> for descriptions of various hallucinogenic substances.

Treatment

A. Emergency and Supportive Measures

Maintain a patent airway and assist respirations if necessary. Treat coma, hyperthermia, hypertension, and seizures as outlined at the beginning of this chapter. For recent large ingestions, consider giving activated charcoal orally or by gastric tube.

B. Specific Treatment

Patients with anticholinergic delirium may benefit from a dose of physostigmine, 0.5–1 mg intravenously, not to exceed 1 mg/min. Dysphoria, agitation, and psychosis associated with LSD or mescaline intoxication may respond

to benzodiazepines (eg, lorazepam, 1–2 mg orally or intravenously) or haloperidol (2–5 mg intramuscularly or intravenously) or another antipsychotic drug (eg, olanzapine or ziprasidone). Monitor patients who have sniffed solvents for cardiac dysrhythmias (most commonly premature ventricular contractions, ventricular tachycardia, ventricular fibrillation); treatment with beta-blockers such as propranolol (1–5 mg intravenously) or esmolol (250–500 mcg/kg intravenously, then 50 mcg/kg/min by infusion) may be more effective than lidocaine or amiodarone.

Tamama K et al. Newly emerging drugs of abuse. *Handb Exp Pharmacol.* 2020;258:463. [PMID: 31595417]

MARIJUANA & SYNTHETIC CANNABINOID

Marijuana refers to the crushed dried leaves and flowers of the Cannabis plant. These dried leaves and flowers contain the psychoactive cannabinoid delta-9-tetrahydrocannabinol (THC), which binds to endogenous cannabinoid receptors. Marijuana is usually smoked in cigarettes or pipes but may also be vaporized or added to a variety of foods, beverages, and candies. Resin from the plant may be dried and pressed into blocks called hashish, and solvents may be used to extract THC into highly concentrated oils (butane hash oil). THC has been used medically as an appetite stimulant, as an antiemetic, and in the treatment of a variety of medical conditions. It has now been legalized for both medical and recreational use in an increasing number of US states (<https://disa.com/map-of-marijuana-legality-by-state>). Toxicity is dose dependent but varies significantly by individual, prior experience, and degree of tolerance. Synthetic cannabinoids ("Spice," "K2," "Black Mamba") are laboratory designed analogs of THC. They have become increasingly popular and are associated with a variety of adverse side effects, including seizures, kidney dysfunction, and serious neuropsychiatric symptoms.

Clinical Findings

Onset of symptoms after smoking is usually rapid (minutes) with a duration of effect of approximately 2 hours. Symptoms may be delayed after ingestion and can result in prolonged intoxication (up to 8 hours). Mild intoxication may result in euphoria, palpitations, heightened sensory awareness, altered time perception, and sedation. More severe intoxication may result in anxiety, visual hallucinations, and acute paranoid psychosis. Physical findings include tachycardia, orthostatic hypotension, conjunctival injection, incoordination, slurred speech, and ataxia. Long-term heavy marijuana use is associated with recurrent nausea, abdominal pain, and vomiting, termed **the cannabinoid hyperemesis syndrome**. Children may inadvertently be exposed to marijuana through the consumption of THC-containing candies or other foods. Children may experience more severe symptoms including stupor, coma, and seizures. E-cigarette or vaping-associated acute lung injury (EVALI) is a syndrome of diffuse lung injury associated with vaping THC adulterated with vitamin E acetate.

Treatment

A. Emergency and Supportive Measures

Treat anxiety and paranoia with simple reassurance and placement into a calming environment. Benzodiazepines such as lorazepam or diazepam may be used for more severe behavioral and psychomotor symptoms. Hypotension and sinus tachycardia should be treated with intravenous fluids.

B. Specific Treatment

There is no specific antidote currently available. Consider activated charcoal early after ingestion of large quantities. Topical capsaicin and haloperidol have been used with variable success for the treatment of acute vomiting in patients with cannabinoid hyperemesis syndrome.

Aldy K et al. E-cigarette or vaping product use-associated lung injury (EVALI) features and recognition in the emergency department. *J Am Coll Emerg Physicians Open.* 2020;1:1090. [PMID: 33145562]

Lucas CJ et al. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol.* 2018;84:2477. [PMID: 30001569]

Wong K et al. Acute cannabis toxicity. *Pediatr Emerg Care.* 2019;35:799. [PMID: 31688799]

MERCURY

Mercury poisoning may occur by ingestion of inorganic mercuric salts, organic mercury compounds, or inhalation of metallic mercury vapor. Ingestion of the mercuric salts causes a burning sensation in the throat, discoloration and edema of oral mucous membranes, abdominal pain, vomiting, bloody diarrhea, and shock. Direct nephrotoxicity causes acute kidney injury. Inhalation of high concentrations of metallic mercury vapor may cause acute fulminant chemical pneumonia. Chronic mercury poisoning causes weakness, ataxia, intention tremors, irritability, and depression. Exposure to alkyl (organic) mercury derivatives from highly contaminated fish or fungicides used on seeds has caused ataxia, tremors, convulsions, and catastrophic birth defects. Nearly all fish have some traces of mercury contamination; the US Environmental Protection Agency (EPA) advises consumers to avoid swordfish, shark, king mackerel, and tilefish because they contain higher levels. Fish and shellfish that are generally low in mercury content include shrimp, canned light tuna (not albacore "white" tuna), salmon, pollock, and catfish. Dental fillings composed of mercury amalgam pose a very small risk of chronic mercury poisoning and their removal is rarely justified. Some imported skin lightening creams contain toxic quantities of mercury.

Treatment

A. Acute Poisoning

There is no effective specific treatment for mercury vapor pneumonitis. Remove ingested mercuric salts by lavage and administer activated charcoal. For acute ingestion of

mercuric salts, give dimercaprol (BAL) at once, as for arsenic poisoning. Unless the patient has severe gastroenteritis, consider succimer (DMSA), 10 mg/kg orally every 8 hours for 5 days and then every 12 hours for 2 weeks. Unithiol (DMPS) is a chelator that can be given orally or parenterally but is not commonly available in the United States; it can be obtained from some compounding pharmacies. Maintain urinary output. Treat oliguria and anuria if they occur.

B. Chronic Poisoning

Remove from exposure. Neurologic toxicity is not considered reversible with chelation, although some authors recommend a trial of succimer or unithiol (contact a regional poison center or medical toxicologist for advice).

Jackson AC. Chronic neurological disease due to methylmercury poisoning. *Can J Neurol Sci.* 2018;45:620. [PMID: 30278852]

Mudan A et al. Notes from the field: methylmercury toxicity from a skin lightening cream obtained from Mexico—California 2019. *MMWR Morb Mortal Wkly Rep.* 2019;68:1166. [PMID: 31856147]

METHANOL & ETHYLENE GLYCOL

Methanol (wood alcohol) is commonly found in a variety of products, including solvents, duplicating fluids, record cleaning solutions, and paint removers. It is sometimes ingested intentionally by alcoholic patients as a substitute for ethanol and may also be found as a contaminant in bootleg whiskey. Ethylene glycol is the major constituent in most antifreeze compounds. The toxicity of both agents is caused by metabolism to highly toxic organic acids—methanol to formic acid; ethylene glycol to glycolic and oxalic acids. Diethylene glycol is a nephrotoxic solvent that has been improperly substituted for glycerine in various liquid medications (cough syrup, teething medicine, acetaminophen), causing numerous deaths in Haiti, Panama, and Nigeria.

Clinical Findings

Shortly after ingestion of methanol or ethylene glycol, patients usually appear “drunk.” The serum osmolality (measured by freezing point depression) is usually increased, but acidosis is often absent early. After several hours, metabolism to toxic organic acids leads to a severe anion gap metabolic acidosis, tachypnea, confusion, convulsions, and coma. Methanol intoxication frequently causes visual disturbances, while ethylene glycol often produces oxalate crystalluria and acute kidney injury. **Note:** Point-of-care analytical devices commonly used in the emergency department may falsely measure glycolic acid (a toxic metabolite of ethylene glycol) as lactic acid.

Treatment

A. Emergency and Supportive Measures

For patients presenting within 30–60 minutes after ingestion, empty the stomach by aspiration through a nasogastric tube. Charcoal is not very effective but should be administered if other poisons or drugs have also been ingested.

B. Specific Treatment

Patients with significant toxicity (manifested by severe metabolic acidosis, altered mental status, markedly elevated osmol gap, or evidence of end-organ toxicity) should undergo hemodialysis as soon as possible to remove the parent compound and the toxic metabolites. Treatment with folic acid, thiamine, and pyridoxine may enhance the breakdown of toxic metabolites.

Ethanol blocks metabolism of the parent compounds by competing for the enzyme alcohol dehydrogenase. Fomepizole (4-methylpyrazole; Antizol) blocks alcohol dehydrogenase and is much easier to use than ethanol. If started before onset of acidosis, fomepizole may be used as the sole treatment for ethylene glycol ingestion in some cases. A regional poison control center (1-800-222-1222) should be contacted for indications and dosing.

Gallagher N et al. The diagnosis and management of toxic alcohol poisoning in the emergency department: a review article. *Adv J Emerg Med.* 2019;3:e28. [PMID: 31410405]

Kraut JA et al. Toxic alcohols. *N Engl J Med.* 2018;378:270. [PMID: 29342392]

Ng PCY et al. Toxic alcohol diagnosis and management: an emergency medicine review. *Intern Emerg Med.* 2018;13:375. [PMID: 29427181]

Pohanka M. Antidotes against methanol poisoning: a review. *Mini Rev Med Chem.* 2019;19:1126. [PMID: 30864518]

METHEMOGLOBINEMIA-INDUCING AGENTS

A large number of chemical agents are capable of oxidizing ferrous hemoglobin to its ferric state (methemoglobin), a form that cannot carry oxygen. Drugs and chemicals known to cause methemoglobinemia include benzocaine (a local anesthetic found in some topical anesthetic sprays and a variety of nonprescription products), aniline, propanil (an herbicide), nitrites, nitrogen oxide gases, nitrobenzene, dapsone, phenazopyridine (Pyridium), and many others. Dapsone has a long elimination half-life and may produce prolonged or recurrent methemoglobinemia. Amyl nitrite and isobutyl nitrite (“poppers”) are inhaled as sexual stimulants but can result in methemoglobinemia.

Clinical Findings

Methemoglobinemia reduces oxygen-carrying capacity and may cause dizziness, nausea, headache, dyspnea, confusion, seizures, and coma. The severity of symptoms depends on the percentage of hemoglobin oxidized to methemoglobin; severe poisoning is usually present when methemoglobin fractions are greater than 40–50%. Even at low levels (15–20%), victims appear cyanotic because of the “chocolate brown” color of methemoglobin, but they have normal PO₂ results on arterial blood gas determinations. Conventional pulse oximetry gives inaccurate oxygen saturation measurements; the reading is often between 85% and 90%. Severe metabolic acidosis may be present. Hemolysis may occur, especially in patients susceptible to oxidant stress (ie, those with glucose-6-phosphate dehydrogenase deficiency).

► Treatment

A. Emergency and Supportive Measures

Administer high-flow oxygen. If the causative agent was recently ingested, administer activated charcoal. Repeated-dose activated charcoal may enhance dapsone elimination.

B. Specific Treatment

Methylene blue enhances the conversion of methemoglobin to hemoglobin by increasing the activity of the enzyme methemoglobin reductase. For symptomatic patients, administer 1–2 mg/kg (0.1–0.2 mL/kg of 1% solution) intravenously. The dose may be repeated once in 15–20 minutes if necessary. Patients with hereditary methemoglobin reductase deficiency or glucose-6-phosphate dehydrogenase deficiency may not respond to methylene blue treatment. In severe cases where methylene blue is not available or is not effective, exchange blood transfusion may be necessary.

Cefalu JN et al. Methemoglobinemia in the operating room and intensive care unit: early recognition, pathophysiology, and management. *Adv Ther*. 2020;37:1714. [PMID: 32193811]
Siendones E et al. Cellular and molecular mechanisms of recessive hereditary methaemoglobinaemia type II. *J Clin Med*. 2018;7:E341. [PMID: 30309019]

MUSHROOMS

There are thousands of mushroom species that cause a variety of toxic effects. The most dangerous species of mushrooms are *Amanita phalloides* and related species, which contain potent cytotoxins (amatoxins). Ingestion of even a portion of one amatoxin-containing mushroom may be sufficient to cause death.

The characteristic pathologic finding in fatalities from amatoxin-containing mushroom poisoning is acute massive necrosis of the liver.

► Clinical Findings

Amatoxin-containing mushrooms typically cause a delayed onset (8–12 hours after ingestion) of severe abdominal cramps, vomiting, and profuse diarrhea, followed in 1–2 days by acute kidney injury, hepatic necrosis, and hepatic encephalopathy. Cooking the mushrooms does *not* prevent poisoning.

Monomethylhydrazine poisoning (*Gyromitra* and *Helvella* species) is more common following ingestion of uncooked mushrooms, as the toxin is water-soluble. Vomiting, diarrhea, hepatic necrosis, convulsions, coma, and hemolysis may occur after a latent period of 8–12 hours.

► Treatment

A. Emergency Measures

After the onset of symptoms, efforts to remove the toxic agent are probably useless, especially in cases of amatoxin or gyromitrin poisoning, where there is usually a delay of 8–12 hours or more before symptoms occur and patients

seek medical attention. However, activated charcoal is recommended for any recent ingestion of an unidentified or potentially toxic mushroom. Administer intravenous fluids liberally to replace massive losses from vomiting and diarrhea; monitor central venous pressure, urinary output, and kidney function tests to help guide volume replacement.

B. Specific Treatment

A variety of purported antidotes (eg, thioctic acid, penicillin, corticosteroids) have been suggested for amatoxin-type mushroom poisoning, but controlled studies are lacking and experimental data in animals are equivocal. Aggressive fluid replacement for diarrhea and intensive supportive care for hepatic failure are the mainstays of treatment. Silymarin (silibinin), a derivative of milk thistle, is commonly used in Europe, but is commercially available in the United States only as an oral nutritional supplement. The European intravenous product (Legalon-SIL) can be obtained in the United States under an emergency IND provided by the FDA. Contact the regional poison control center (1-800-222-1222) for more information. *N*-acetylcysteine has also been used and may provide some benefit. Liver transplant may be the only hope for survival in gravely ill patients—contact a liver transplant center early.

Liu J et al. *N*-acetylcysteine as a treatment for amatoxin poisoning: a systematic review. *Clin Toxicol (Phila)*. 2020;58:1015. [PMID: 32609548]

White J et al. Mushroom poisoning: a proposed new clinical classification. *Toxicon*. 2019;157:53. [PMID: 30439442]

OPIATES & OPIOIDS

Prescription and illicit opiates and opioids (morphine, heroin, codeine, oxycodone, fentanyl, hydromorphone, etc) are popular drugs of misuse and abuse and the cause of frequent hospitalizations for overdose. These drugs have widely varying potencies and durations of action; for example, some of the illicit fentanyl derivatives are up to 2000 times more potent than morphine. Poisonings and fatalities have been reported due to the illicit use of fentanyl and the presence of fentanyl and its derivatives in counterfeit medications. All of these agents decrease central nervous system activity and sympathetic outflow by acting on opiate receptors in the brain. Tramadol is an analgesic that is unrelated chemically to the opioids but acts on opioid receptors. Buprenorphine is a partial agonist-antagonist opioid used for the outpatient treatment of both chronic pain and opioid addiction (Table 5–6). Kratom (*Mitragyna speciosa*) is an herbal supplement with agonist activity at mu opioid receptors. While it has been marketed as a “safe” and natural treatment for patients with opioid use disorder, overdose is associated with both agitation and drowsiness and in severe cases seizures, hallucinations, and respiratory depression.

► Clinical Findings

Mild intoxication is characterized by euphoria, drowsiness, and constricted pupils. More severe intoxication may cause hypotension, bradycardia, hypothermia, coma, and

respiratory arrest. Pulmonary edema may occur. Death is usually due to apnea or pulmonary aspiration of gastric contents. Methadone may cause QT interval prolongation and torsades de pointes. While the duration of effect for heroin is usually 3–5 hours, methadone intoxication may last for 48–72 hours or longer. Tramadol, dextromethorphan, and meperidine also occasionally cause seizures. With meperidine, the metabolite normeperidine is probably the cause of seizures and is most likely to accumulate with repeated dosing in patients with chronic kidney disease. Wound botulism has been associated with skin-popping, especially involving “black tar” heroin. Buprenorphine added to an opioid regimen may precipitate acute withdrawal symptoms. Many opioids, including fentanyl, tramadol, oxycodone, and methadone, are not detected on routine urine toxicology “opiate” screening.

► Treatment

A. Emergency and Supportive Measures

Protect the airway and assist ventilation. Administer activated charcoal for recent large ingestions.

B. Specific Treatment

Naloxone is a specific opioid antagonist that can rapidly reverse signs of narcotic intoxication. Although it is structurally related to the opioids, it has no agonist effects of its own. If no intravenous access is available, administer naloxone 4 mg intranasally, otherwise administer 0.2–2 mg intravenously and repeat as needed to awaken the patient and maintain airway protective reflexes and spontaneous breathing. Large doses (up to 10 mg) may be required for patients intoxicated by some opioids (eg, codeine, fentanyl derivatives). **Caution:** The duration of effect of naloxone is only about 2–3 hours; *repeated doses* may be necessary for patients intoxicated by long-acting drugs such as methadone. Continuous observation for at least 3 hours after the last naloxone dose is mandatory.

Bauman MH et al. U-47700 and its analogs: non-fentanyl synthetic opioids impacting the recreational drug market. *Brain Sci.* 2020;10:895. [PMID: 33238449]

Jones CM. Changes in synthetic opioid involvement in drug overdose deaths in the United States, 2010–2016. *JAMA.* 2018;319:1819. [PMID: 29715347]

Lavonas EJ et al. Impact of the opioid epidemic. *Crit Care Clin.* 2020;36:753. [PMID: 32892827]

There are a variety of chemical agents in this group, with widely varying potencies. Most of them are poorly water-soluble, are often formulated with an aromatic hydrocarbon solvent such as xylene and are well absorbed through intact skin. Most chemical warfare “nerve agents” (such as GA [tabun], GB [sarin], GD [soman], and VX) are organophosphates.

► Clinical Findings

Inhibition of cholinesterase results in abdominal cramps, diarrhea, vomiting, excessive salivation, sweating, lacrimation, miosis, wheezing and bronchorrhea, seizures, and skeletal muscle weakness. Initial tachycardia is usually followed by bradycardia. Profound skeletal muscle weakness, aggravated by excessive bronchial secretions and wheezing, may result in respiratory arrest and death. Symptoms and signs of poisoning may persist or recur over several days, especially with highly lipid-soluble agents such as fenthion or dimethoate.

The diagnosis should be suspected in patients who present with miosis, sweating, and diarrhea. Serum and red blood cell cholinesterase activity is usually depressed at least 50% below baseline in those victims who have severe intoxication.

► Treatment

A. Emergency and Supportive Measures

If the agent was recently ingested, consider gut decontamination by aspiration of the liquid using a nasogastric tube followed by administration of activated charcoal. If the agent is on the victim's skin or hair, wash repeatedly with soap or shampoo and water. Providers should take care to avoid skin exposure by wearing gloves and waterproof aprons. Dilute hypochlorite solution (eg, household bleach diluted 1:10) is reported to help break down organophosphate pesticides and nerve agents on equipment or clothing.

B. Specific Treatment

Atropine reverses excessive muscarinic stimulation and is effective for treatment of salivation, bronchial hypersecretion, wheezing, abdominal cramping, and sweating. However, it does not interact with nicotinic receptors at autonomic ganglia and at the neuromuscular junction and has no direct effect on muscle weakness. Administer 2 mg intravenously, and if there is no response after 5 minutes, give repeated boluses in rapidly escalating doses (eg, doubling the dose each time) as needed to dry bronchial secretions and decrease wheezing; as much as several hundred milligrams of atropine have been given to treat severe poisoning.

Pralidoxime (2-PAM, Protopam) is a more specific antidote that reverses organophosphate binding to the cholinesterase enzyme; therefore, it should be effective at the neuromuscular junction as well as other nicotinic and muscarinic sites. It is most likely to be clinically effective if started very soon after poisoning, to prevent permanent binding of the organophosphate to cholinesterase. However, clinical studies have yielded conflicting results regarding the effectiveness of pralidoxime in reducing mortality.

PESTICIDES: CHOLINESTERASE INHIBITORS

Organophosphorus and carbamate insecticides (organophosphates: parathion, malathion, etc; carbamates: carbaryl, aldicarb, etc) are widely used in commercial agriculture and home gardening and have largely replaced older, more environmentally persistent organochlorine compounds such as DDT and chlordane. The organophosphates and carbamates—also called anticholinesterases because they inhibit the enzyme acetylcholinesterase—cause an increase in acetylcholine activity at **nicotinic** and **muscarinic** receptors and in the peripheral and central nervous system.

Administer 1–2 g intravenously as a loading dose and begin a continuous infusion (200–500 mg/h, titrated to clinical response). Continue to give pralidoxime as long as there is any evidence of acetylcholine excess. Pralidoxime is of questionable benefit for carbamate poisoning, because carbamates have only a transitory effect on the cholinesterase enzyme. Other, unproven therapies for organophosphate poisoning include magnesium, sodium bicarbonate, clonidine, and extracorporeal removal.

Hulse EJ et al. Organophosphorus nerve agent poisoning: managing the poisoned patient. Br J Anaesth. 2019;123:457. [PMID: 31248646]

Kharel H et al. The efficacy of pralidoxime in the treatment of organophosphate poisoning in humans: a systematic review and meta-analysis of randomized controlled trials. Cureus. 2020;12:e1714. [PMID: 32257715]

PETROLEUM DISTILLATES & SOLVENTS

Petroleum distillate toxicity may occur from inhalation of the vapor or as a result of pulmonary aspiration of the liquid during or after ingestion. Acute manifestations of aspiration pneumonitis are vomiting, coughing, and bronchopneumonia. Some hydrocarbons—ie, those with aromatic or halogenated subunits—can also cause severe systemic poisoning after oral ingestion. Hydrocarbons can also cause systemic intoxication by inhalation. Vertigo, muscular incoordination, irregular pulse, myoclonus, and seizures occur with serious poisoning and may be due to hypoxemia or the systemic effects of the agents. Chlorinated and fluorinated hydrocarbons (trichloroethylene, Freons, etc) and many other hydrocarbons can cause ventricular arrhythmias due to increased sensitivity of the myocardium to the effects of endogenous catecholamines.

Treatment

Remove the patient to fresh air. For simple aliphatic hydrocarbon ingestion, gastric emptying and activated charcoal are not recommended, but these procedures may be indicated if the preparation contains toxic solutes (eg, an insecticide) or is an aromatic or halogenated product. Observe the victim for 6–8 hours for signs of aspiration pneumonitis (cough, localized crackles or rhonchi, tachypnea, and infiltrates on chest radiograph). Corticosteroids are not recommended. If fever occurs, give a specific antibiotic only after identification of bacterial pathogens by laboratory studies. Because of the risk of arrhythmias, use bronchodilators with caution in patients with chlorinated or fluorinated solvent intoxication. If tachyarrhythmias occur, use esmolol intravenously 25–100 mcg/kg/min.

Forrester MB. Computer and electronic duster spray inhalation (huffing) injuries managed at emergency departments. Am J Drug Alcohol Abuse. 2020;46:180. [PMID: 31449429]

SALICYLATES

Salicylates (aspirin, methyl salicylate, bismuth subsalicylate, etc) are found in a variety of over-the-counter and prescription medications. Salicylates uncouple cellular

oxidative phosphorylation, resulting in anaerobic metabolism and excessive production of lactic acid and heat, and they also interfere with several Krebs cycle enzymes. A single ingestion of more than 200 mg/kg of salicylate is likely to produce significant acute intoxication. Poisoning may also occur as a result of chronic excessive dosing over several days. Although the half-life of salicylate is 2–3 hours after small doses, it may increase to 20 hours or more in patients with intoxication.

Clinical Findings

Acute ingestion often causes nausea and vomiting, occasionally with gastritis. Moderate intoxication is characterized by hyperpnea (deep and rapid breathing), tachycardia, tinnitus, and elevated anion gap metabolic acidosis. (A normal anion gap sometimes occurs due to salicylate interference with the chemistry analyzer, falsely raising the measured chloride.) Serious intoxication may result in agitation, confusion, coma, seizures, cardiovascular collapse, pulmonary edema, hyperthermia, and death. The prothrombin time is often elevated owing to salicylate-induced hypoprothrombinemia. Central nervous system intracellular glucose depletion can occur despite normal measured serum glucose levels.

Diagnosis of salicylate poisoning is suspected in any patient with metabolic acidosis and is confirmed by measuring the serum salicylate level. Patients with levels greater than 100 mg/dL (1000 mg/L or 7.2 mcmol/L) after an acute overdose are more likely to have severe poisoning. On the other hand, patients with subacute or chronic intoxication may suffer severe symptoms with levels of only 60–70 mg/dL (4.3–5 mcmol/L). The arterial blood gas typically reveals a respiratory alkalosis with an underlying metabolic acidosis.

Treatment

A. Emergency and Supportive Measures

Administer activated charcoal orally. Gastric lavage followed by administration of extra doses of activated charcoal may be needed in patients who ingest more than 10 g of aspirin. The desired ratio of charcoal to aspirin is about 10:1 by weight; while this cannot always be given as a single dose, it may be administered over the first 24 hours in divided doses every 2–4 hours along with whole bowel irrigation. Give glucose-containing fluids to reduce the risk of cerebral hypoglycemia. Treat metabolic acidosis with intravenous sodium bicarbonate. This is critical because acidosis (especially acidemia, pH < 7.40) promotes greater entry of salicylate into cells, worsening toxicity. **Warning:** Sudden and severe deterioration can occur after rapid sequence intubation and controlled ventilation if the pH is allowed to fall due to hypercarbia during the apneic period.

B. Specific Treatment

Alkalization of the urine enhances renal salicylate excretion by trapping the salicylate anion in the urine. Add 100 mEq (two ampules) of sodium bicarbonate to 1 L of 5% dextrose in 0.2% saline, and infuse this solution

Table 38–8. Common seafood poisonings (listed in alphabetical order).

Type of Poisoning	Mechanism	Clinical Presentation
Ciguatera	Reef fish ingest toxic dinoflagellates, whose toxins accumulate in fish meat. Commonly implicated fish in the United States are barracuda, jack, snapper, and grouper.	1–6 hours after ingestion, victims develop abdominal pain, vomiting, and diarrhea accompanied by a variety of neurologic symptoms, including paresthesias, reversal of hot and cold sensation, vertigo, headache, and intense itching. Autonomic disturbances, including hypotension and bradycardia, may occur.
Paralytic shellfish poisoning	Dinoflagellates produce saxitoxin, which is concentrated by filter-feeding mussels and clams. Saxitoxin blocks sodium conductance and neuronal transmission in skeletal muscles.	Onset is usually within 30–60 minutes. Initial symptoms include perioral and intraoral paresthesias. Other symptoms include nausea and vomiting, headache, dizziness, dysphagia, dysarthria, ataxia, and rapidly progressive muscle weakness that may result in respiratory arrest.
Puffer fish poisoning	Tetrodotoxin is concentrated in liver, gonads, intestine, and skin. Toxic effects are similar to those of saxitoxin. Tetrodotoxin is also found in some North American newts and Central American frogs.	Onset is usually within 30–40 minutes but may be as short as 10 minutes. Initial perioral paresthesias are followed by headache, diaphoresis, nausea, vomiting, ataxia, and rapidly progressive muscle weakness that may result in respiratory arrest.
Scombroid	Improper preservation of large fish results in bacterial degradation of histidine to histamine. Commonly implicated fish include tuna, mahimahi, bonita, mackerel, and kingfish.	Allergic-like (anaphylactoid) symptoms are due to histamine, usually begin within 15–90 minutes, and include skin flushing, itching, urticaria, angioedema, bronchospasm, and hypotension as well as abdominal pain, vomiting, and diarrhea.

intravenously at a rate of about 150–200 mL/h. Unless the patient is oliguric or hyperkalemic, add 20–30 mEq of potassium chloride to each liter of intravenous fluid. Patients who are volume-depleted often fail to produce an alkaline urine (paradoxical aciduria) unless potassium is given.

Hemodialysis may be lifesaving and is indicated for patients with severe metabolic acidosis, markedly altered mental status, or significantly elevated salicylate levels (eg, greater than 100–120 mg/dL [1000–1200 mg/L or 7.2–8.6 mcmol/L] after acute overdose or greater than 60–70 mg/dL [600–700 mg/L or 4.3–5 mcmmol/L] with subacute or chronic intoxication).

Bowers D et al. Managing acute salicylate toxicity in the emergency department. *Adv Emerg Nurs J.* 2019;41:76. [PMID: 30702537]
Palmer BF et al. Salicylate toxicity. *N Engl J Med.* 2020;382:2544. [PMID: 32579814]

SEAFOOD POISONINGS

A variety of intoxications may occur after eating certain types of fish or other seafood. These include scombroid, ciguatera, paralytic shellfish, and puffer fish poisoning. The mechanisms of toxicity and clinical presentations are described in Table 38–8. In the majority of cases, the seafood has a normal appearance and taste (scombroid may have a peppery taste).

Treatment

A. Emergency and Supportive Measures

Caution: Abrupt respiratory arrest may occur in patients with acute paralytic shellfish and puffer fish poisoning.

Observe patients for at least 4–6 hours. Replace fluid and electrolyte losses from gastroenteritis with intravenous saline or other crystalloid solution.

For recent ingestions, it may be possible to adsorb residual toxin in the gut with activated charcoal, 50–60 g orally.

B. Specific Treatment

There is no specific antidote for paralytic shellfish or puffer fish poisoning.

1. Ciguatera—There are anecdotal reports of successful treatment of acute neurologic symptoms with mannitol, 1 g/kg intravenously, but this approach is not widely accepted.

2. Scombroid—Antihistamines such as diphenhydramine, 25–50 mg intravenously, and the H₂-blocker cimetidine, 300 mg intravenously, are usually effective.

Chinain M et al. Ciguatera poisoning in French Polynesia: insights into the novel trends of an ancient disease. *New Microbes New Infect.* 2019;31:100565. [PMID: 31312457]
Colombo FM et al. Histamine food poisonings: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr.* 2018;58:1131. [PMID: 27791395]

Warrell DA. Venomous bites, stings, and poisoning: an update. *Infect Dis Clin North Am.* 2019;33:17. [PMID: 30712761]

SNAKE BITES

The venom of poisonous snakes and lizards may be predominantly **neurotoxic** (coral snake) or predominantly **cytolytic** (rattlesnakes, other pit vipers). Neurotoxins cause respiratory paralysis; cytolytic venoms cause tissue destruction by digestion and hemorrhage due to hemolysis and destruction of the endothelial lining of the blood vessels.

The manifestations of rattlesnake envenomation are mostly local pain, redness, swelling, and extravasation of blood. Perioral tingling, metallic taste, nausea and vomiting, hypotension, and coagulopathy may also occur. Thrombocytopenia can persist for several days after a rattlesnake bite. Neurotoxic envenomation may cause ptosis, dysphagia, diplopia, and respiratory arrest.

► Treatment

A. Emergency Measures

Immobilize the patient and the bitten part in a neutral position. Avoid manipulation of the bitten area. Transport the patient to a medical facility for definitive treatment. Do *not* give alcoholic beverages or stimulants; do *not* apply ice; do *not* apply a tourniquet. The potential trauma to underlying tissues resulting from incision and suction performed by unskilled people is probably not justified in view of the small amount of venom that can be recovered.

B. Specific Antidote and General Measures

1. Pit viper (eg, rattlesnake) envenomation—There are two commercially available antivenins for rattlesnake envenomation (CroFab and Anavip). Depending on the severity of symptoms CroFab is administered in increments of 4–6 vials by slow intravenous drip in 250–500 mL saline. For more serious envenomation with marked local effects and systemic toxicity (eg, hypotension, coagulopathy), higher doses and additional vials may be required. The dosing of Anavip is 10 vials by slow intravenous infusion over 60 minutes initially followed by additional 10-vial increments as needed for more serious envenomations or for progression of symptoms. Monitor vital signs and the blood coagulation profile. Type and cross-match blood. The adequacy of venom neutralization is indicated by improvement in symptoms and signs, and the rate that swelling slows. Prophylactic antibiotics are not indicated after a rattlesnake bite.

2. Elapid (coral snake) envenomation—Give 1–2 vials of specific antivenom as soon as possible. **Note:** Pfizer/Wyeth no longer makes coral snake antivenom in the United States and remaining supplies are dwindling. To locate antisera for this or exotic snakes, call a regional poison control center (1-800-222-1222).

August JA et al. Prophylactic antibiotics are not needed following rattlesnake bites. Am J Med. 2018;131:1367. [PMID: 30392637]

Mascarenhas D et al. Comparison of F(ab')₂ and Fab antivenoms in rattlesnake envenomation: first year's post-marketing experience with F(ab')₂ in New Mexico. Toxicology. 2020;186:42. [PMID: 32763251]

Waiddyanatha S et al. Long-term effects of snake envenoming. Toxins (Basel). 2019;11:E193. [PMID: 30935096]

Warrell DA. Venomous bites, stings, and poisoning: an update. Infect Dis Clin North Am. 2019;33:17. [PMID: 30712761]

SPIDER BITES & SCORPION STINGS

Envenomation from most species of spiders in the United States causes only local pain, redness, and swelling. The more venomous black widow spiders (*Latrodectus mactans*)

cause generalized muscular pains, muscle spasms, and rigidity. The brown recluse spider (*Loxosceles reclusa*) causes progressive local necrosis as well as hemolytic reactions (rare).

Stings by most scorpions in the United States cause only local pain. Stings by the more toxic *Centruroides* species (found in the southwestern United States) may cause muscle cramps, twitching and jerking, and occasionally hypertension, convulsions, and pulmonary edema. Stings by scorpions from other parts of the world are not discussed here.

► Treatment

A. Black Widow Spider Bites

Pain may be relieved with parenteral opioids or muscle relaxants (eg, methocarbamol, 15 mg/kg). Calcium gluconate 10%, 0.1–0.2 mL/kg intravenously, may transiently relieve muscle rigidity, though its effectiveness is unproven. *Latrodectus* antivenom is possibly more effective, but because of concerns about acute hypersensitivity reactions (horse serum-derived), it is often reserved for very young or elderly patients or those who do not respond promptly to the above measures. Horse serum sensitivity testing is required. (Instruction and testing materials are included in the antivenin kit.)

B. Brown Recluse Spider Bites

Because bites occasionally progress to extensive local necrosis, some authorities recommend early excision of the bite site, whereas others use oral corticosteroids. Anecdotal reports have claimed success with dapsone and colchicine. All of these treatments remain unproven.

C. Scorpion Stings

No specific treatment other than analgesics is required for envenomations by most scorpions found in the United States. An FDA-approved specific antivenom is available for *Centruroides* stings.

Glatstein M et al. Treatment of pediatric black widow spider envenomation: a national poison center's experience. Am J Emerg Med. 2018;36:998. [PMID: 29133072]

Warrell DA. Venomous bites, stings, and poisoning: an update. Infect Dis Clin North Am. 2019;33:17. [PMID: 30712761]

THEOPHYLLINE & CAFFEINE

Methylxanthines, including theophylline and caffeine, are nonselective adenosine receptor antagonists. In overdose, toxicity results from the release of endogenous catecholamines with beta-1- and beta-2-adrenergic stimulation. Theophylline may cause intoxication after an acute single overdose, or intoxication may occur as a result of chronic accidental repeated overmedication or reduced elimination resulting from hepatic dysfunction or interacting drug (eg, cimetidine, erythromycin). The usual serum half-life of theophylline is 4–6 hours, but this may increase to more than 20 hours after overdose. Caffeine in energy drinks or

herbal or dietary supplement products can produce similar toxicity.

► Clinical Findings

Mild intoxication causes nausea, vomiting, tachycardia, and tremulousness. Severe intoxication is characterized by ventricular and supraventricular tachyarrhythmias, hypotension, and seizures. Status epilepticus is common and often intractable to the usual anticonvulsants. After acute overdose (but not chronic intoxication), hypokalemia, hyperglycemia, and metabolic acidosis are common. Seizures and other manifestations of toxicity may be delayed for several hours after acute ingestion, especially if a sustained-release preparation such as Theo-Dur was taken.

Diagnosis is based on measurement of the serum theophylline concentration. Seizures and hypotension are likely to develop in acute overdose patients with serum levels greater than 100 mg/L (555 mcmol/L). Serious toxicity may develop at lower levels (ie, 40–60 mg/L [222–333 mcmol/L]) in patients with chronic intoxication. Serum caffeine levels are not routinely available in clinical practice, but in a study of 51 fatal cases the median level was 180 mg/L (range 33–567 mg/L).

► Treatment

A. Emergency and Supportive Measures

After acute ingestion, administer activated charcoal. Repeated doses of activated charcoal may enhance theophylline elimination by “gut dialysis.” Addition of whole bowel irrigation should be considered for large ingestions involving sustained-release preparations.

Hemodialysis is effective in removing theophylline and is indicated for patients with status epilepticus or markedly elevated serum theophylline levels (eg, greater than 100 mg/L [555 mcmol/L] after acute overdose or greater than 60 mg/L [333 mcmol/L] with chronic intoxication).

B. Specific Treatment

Treat seizures with benzodiazepines (lorazepam, 2–3 mg intravenously, or diazepam, 5–10 mg intravenously) or phenobarbital (10–15 mg/kg intravenously). Phenytoin is not effective. Hypotension and tachycardia—which are mediated through excessive beta-adrenergic stimulation—may respond to beta-blocker therapy even in low doses. Administer esmolol, 25–50 mcg/kg/min by intravenous infusion, or propranolol, 0.5–1 mg intravenously.

TRICYCLIC & OTHER ANTIDEPRESSANTS

Tricyclic and related cyclic antidepressants are among the most dangerous drugs involved in suicidal overdose. These drugs have anticholinergic and cardiac depressant properties (“quinidine-like” sodium channel blockade). Tricyclic antidepressants produce more marked membrane-depressant cardiotoxic effects than the phenothiazines.

Newer-generation antidepressants such as trazodone, fluoxetine, citalopram, paroxetine, sertraline, bupropion, venlafaxine, and fluvoxamine are not chemically related to the tricyclic antidepressant agents and, with the exception of bupropion, do not generally produce quinidine-like cardiotoxic effects. However, they may cause seizures in overdoses and they may cause **serotonin syndrome**.

► Clinical Findings

Signs of severe intoxication may occur abruptly and without warning within 30–60 minutes after acute tricyclic overdose. Anticholinergic effects include dilated pupils, tachycardia, dry mouth, flushed skin, muscle twitching, and decreased peristalsis. Quinidine-like cardiotoxic effects include QRS interval widening (greater than 0.12 s; Figure 38–2), ventricular arrhythmias, AV block, and hypotension. Rightward-axis deviation of the terminal 40 ms of the QRS has also been described. Prolongation of the QT interval and torsades de pointes have been reported with several of the newer antidepressants. Seizures and coma are common with severe intoxication. Life-threatening hyperthermia may result from status epilepticus and anti-cholinergic-induced impairment of sweating. Among newer agents, bupropion and venlafaxine have been associated with a greater risk of seizures.



▲ Figure 38–2. Cardiac arrhythmias resulting from tricyclic antidepressant overdose. **A:** Delayed intraventricular conduction results in prolonged QRS interval (0.18 s). **B** and **C:** Supraventricular tachycardia with progressive widening of QRS complexes mimics ventricular tachycardia. (Reproduced, with permission, from Benowitz NL, Goldschlager N. Cardiac disturbances in the toxicologic patient. In: Haddad LM, Winchester JF [editors], *Clinical Management of Poisoning and Drug Overdose*, 3rd edition. Saunders/Elsevier, 1998. Copyright © Elsevier.)

Aggelopoulos E et al. Atrial fibrillation and shock: unmasking theophylline toxicity. *Med Princ Pract*. 2018;27:387. [PMID: 29936503]

Carreon CC et al. How to recognize caffeine overdose. *Nursing*. 2019;49:52. [PMID: 30893206]

Kato Y et al. Extracorporeal membrane oxygenation for hypokalemia and refractory ventricular fibrillation associated with caffeine intoxication. *J Emerg Med*. 2020;58:59. [PMID: 31740156]

Koh BA et al. Acute intentional caffeine overdose treated preemptively with hemodialysis. *Am J Emerg Med*. 2020;38:692.e1. [PMID: 31785982]

The diagnosis should be suspected in any overdose patient with anticholinergic side effects, especially if there is widening of the QRS interval or seizures. For intoxication by most tricyclic antidepressants, the QRS interval correlates with the severity of intoxication more reliably than the serum drug level.

Serotonin syndrome should be suspected if agitation, delirium, diaphoresis, tremor, hyperreflexia, clonus (spontaneous, inducible, or ocular), and fever develop in a patient taking serotonin reuptake inhibitors.

Treatment

A. Emergency and Supportive Measures

Observe patients for at least 6 hours and admit all patients with evidence of anticholinergic effects (eg, delirium, dilated pupils, tachycardia) or signs of cardiotoxicity.

Administer activated charcoal and consider gastric lavage after recent large ingestions. All of these drugs have large volumes of distribution and are not effectively removed by hemodialysis procedures.

B. Specific Treatment

Cardiotoxic sodium channel-depressant effects of tricyclic antidepressants may respond to boluses of sodium

bicarbonate (50–100 mEq intravenously). Sodium bicarbonate provides a large sodium load that alleviates depression of the sodium-dependent channel. Reversal of acidosis may also have beneficial effects at this site. Maintain the pH between 7.45 and 7.50. Alkalization does not promote excretion of tricyclic antidepressants. Prolongation of the QT interval or torsades de pointes is usually treated with intravenous magnesium or overdrive pacing. Severe cardiotoxicity in patients with overdoses of lipid-soluble drugs (eg, amitriptyline, bupropion) has reportedly responded to intravenous lipid emulsion (Intralipid), 1.5 mL/kg repeated one or two times if needed. Plasma exchange using albumin and ECMO have been reported to be successful in several cases.

Mild serotonin syndrome may be treated with benzodiazepines and withdrawal of the antidepressant. Moderate cases may respond to cyproheptadine (4 mg orally or via gastric tube hourly for three or four doses) or chlorpromazine (25 mg intravenously). Severe hyperthermia should be treated with neuromuscular paralysis and endotracheal intubation in addition to external cooling measures.

Butt K et al. A peculiar wide complex tachycardia. Circulation. 2019;139:1454. [PMID: 30856002]

39

Cancer

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INTRODUCTION TO CANCER

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Etiology

Cancer is the second most common cause of death in the United States. In 2020, an estimated 1,806,590 cases of cancer were diagnosed, and 606,520 persons died of cancer. Based on current statistics, almost 40% of Americans will be diagnosed with cancer at some point during their lifetime. Table 39–1 lists the 10 leading cancer types in men and women by site.

However, death rates from cancers are declining. Compared to the 1991 overall cancer death rate of 215.1 per 100,000 population, the 2017 rate of 152.4 per 100,000 represents a 29% reduction in the overall cancer death rate. Importantly, death rates have declined in all four of the most common cancer types (lung, colorectum, breast, and prostate). Reductions in cancer mortality reflect successful implementation of a broad strategy of prevention, detection, and treatment. Due to these improvements, the number of cancer survivors is increasing. In 2015, an estimated 14.5 million people were alive in whom cancer had been previously diagnosed; that number is projected to grow to 18.9 million in 2024.

Modifiable Risk Factors

Tobacco is the most common preventable cause of cancer death; at least 30% of all cancer deaths in the United States are directly linked to tobacco. In 2014, an estimated 167,133 cancer deaths in the United States could be directly attributed to tobacco. Clear evidence links tobacco use to at least 15 cancers. The most dramatic link is with lung cancer; 80% of lung cancer deaths are attributable to smoking. Remarkably, almost 10% of long-term survivors of a tobacco-related cancer continue to use tobacco products, increasing their risk of yet another cancer.

The prevalence of smoking for US adults based on the 2019 National Health Interview Survey is 14% for adults aged 18 and older, which is a remarkable reduction from

the 1955 peak of 57% for males and the 1965 peak of 34% for females. Cigarettes are the most common form of tobacco used in the United States, though the use of non-cigarette forms of tobacco and of electronic cigarettes is increasing. Electronic cigarette aerosol can contain harmful substances, including nicotine, heavy metals, volatile organic compounds, and carcinogenic substances. The use of flavoring compounds increases the attractiveness of these devices to youth raising the concern that these devices will encourage youth to transition to cigarettes. In 2020, the percent age of US high school students who used e-cigarettes in the past 30 days was approximately 19.6%.

Tobacco cessation directed toward the individual should start with clinician counseling. Simple, concise advice from a clinician can yield cessation rates of 10–20%. Additive strategies include more intensive counseling; nicotine replacement therapy with patches, gum, lozenges, or inhalers; and prescription medication with bupropion or varenicline (see Chapter 1).

For those Americans who do not use tobacco, the most modifiable risk factors are nutrition and physical activity. Prudent recommendations to reduce cancer risk are to (1) avoid tobacco; (2) be physically active; (3) maintain a healthy weight; (4) consume a diet rich in fruits, vegetables, and whole grains; (5) lower consumption of saturated and trans dietary fats; (6) limit alcohol use; and (7) avoid excess sun exposure.

Another modifiable cancer risk factor is radiation from radiographic studies. A 2009 study reported that the use of computed tomography (CT) in diagnostic algorithms exposes individuals to significant radiation doses that may increase their lifetime risk of cancer. Both standardization of CT radiation doses and limiting testing have been important steps in minimizing this risk.

American Cancer Society. Cancer Facts & Figures 2021. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf>

Centers for Disease Control and Prevention (CDC). Smoking & Tobacco Use: About Electronic Cigarettes (E-Cigarettes). https://www.cdc.gov/tobacco/basic_information/e-cigarettes/index.htm

Table 39–1. Estimated 10 most common cancer cases in the United States in males and females (all races).

Rank	Males	Females
	Total Cases [N] = 970,250 (100 percent)	Total Cases [N] = 927,910 (100 percent)
1	Prostate 248,530 (26)	Breast 281,550 (30)
2	Lung and bronchus 119,100 (12)	Lung and bronchus 116,660 (13)
3	Colon and rectum 79,520 (8)	Colon and rectum 69,980 (8)
4	Urinary bladder 64,280 (7)	Uterine corpus 66,570 (7)
5	Melanoma 62,260 (6)	Melanoma 43,850 (5)
6	Kidney and renal pelvis 48,780 (5)	Non-Hodgkin lymphoma 35,930 (4)
7	Non-Hodgkin lymphoma 45,630 (5)	Thyroid 32,130 (3)
8	Oral cavity and pharynx 38,800 (4)	Pancreas 28,480 (3)
9	Leukemia 35,530 (4)	Kidney and renal pelvis 27,300 (3)
10	Pancreas 31,950 (3)	Leukemia 25,560 (3)
	Other sites 195,870 (20)	Other sites 199,900 (21)

Data from the American Cancer Society, 2021.

Office of Disease Prevention and Health Promotion. Healthy People 2030. Tobacco use objectives: reduce tobacco use in adults. <https://health.gov/healthypeople/objectives-and-data/browse-objectives/tobacco-use/reduce-current-tobacco-use-adults-tu-01>

Klein WMP et al. Alcohol and cancer risk: clinical and research implications. JAMA. 2020;323:23. [PMID: 31834355]
Siegel RL et al. Cancer statistics, 2021. CA Cancer J Clin. 2021; 71:7. [PMID: 33433946]

► Staging

The TNM system is the commonly used classification to stage cancer. Staging is important not only because it correlates with the patient's long-term survival but also because it is used to determine which patients should receive adjuvant or neoadjuvant therapy.

Certain characteristics of cancers, not reflected in the TNM stage, may be used to indicate prognosis and guide treatment. Pathologic features seen on routine histologic examination for some cancers are very important; examples include the Gleason score for prostate cancer, human papillomavirus (HPV) status of oropharyngeal cancer, and grade of sarcomas. Cancer specimens should also be sent for molecular diagnostic testing and programmed death-ligand 1 (PD-L1) expression testing when appropriate. Some examples of targeted molecular testing include *HER2* in breast and gastric cancer, *K-ras* and *BRAF* mutations in colorectal cancer and melanoma, and epidermal growth factor receptor (EGFR) and fusion genes (*ALK* and *ROS1*) in lung cancer.

Machczyński P et al. A review of the 8th edition of the AJCC staging system for oropharyngeal cancer according to HPV status. Eur Arch Otorhinolaryngol. 2020;277:2407. [PMID: 32342197]

► Treatment

See Primary Cancer Treatment section below. Table 39–2 outlines treatment choices by cancer type for those responsive to systemic agents, and Table 39–3 provides a listing of common chemotherapeutic agents.

Table 39–2. Treatment choices for cancers responsive to systemic agents.

Diagnosis	Initial Treatment
Acute lymphoblastic leukemia (ALL)	Induction combination chemotherapy (Philadelphia chromosome-positive): Cyclophosphamide, vincristine, doxorubicin/daunorubicin, dexamethasone (hyper-CVAD) alternating with cytarabine, methotrexate; add imatinib or dasatinib or nilotinib Induction combination chemotherapy (Philadelphia chromosome-negative): Daunorubicin, vincristine, prednisone, pegaspargase, cyclophosphamide; or hyper-CVAD alternating with methotrexate and cytarabine Maintenance chemotherapy: Methotrexate, 6-mercaptopurine, vincristine, prednisone
Acute myeloid leukemia (AML)	Induction combination chemotherapy: Cytarabine with daunorubicin or idarubicin, with gemtuzumab ozogamicin (CD33-positive), or with midostaurin (<i>FLT3</i> -mutated), or with fludarabine Alternative chemotherapy for ≥ 60 years old: Azacitidine, decitabine, or low-dose cytarabine with or without venetoclax; or Liposomal encapsulation of cytarabine and daunorubicin (therapy-related or myelodysplasia-related changes) Ivosidenib (<i>IDH1</i> mutation); or Enasidenib (<i>IDH2</i> mutation)

(continued)

Table 39–2. Treatment choices for cancers responsive to systemic agents. (continued)

Diagnosis	Initial Treatment
Chronic myeloid leukemia (CML)	Nilotinib or dasatinib or imatinib or bosutinib
Chronic lymphocytic leukemia (CLL)	Venetoclax with obinutuzumab, or acalabrutinib with or without obinutuzumab, or ibrutinib
Hairy cell leukemia	Cladribine with or without rituximab ¹ or pentostatin
Hodgkin lymphoma	Combination chemotherapy: Doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD), or Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP)
Non-Hodgkin lymphoma (intermediate and high grade)	Combination chemotherapy: Cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab ¹ (CHOP-R), or Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab ¹ (dose-adjusted R-EPOCH) (for double-/triple-hit)
Non-Hodgkin lymphoma (low grade)	Combination chemotherapy: Bendamustine plus obinutuzumab or rituximab ¹ , or Cyclophosphamide, vincristine, doxorubicin, prednisone, rituximab ¹ (CHOP-R), or Cyclophosphamide, vincristine, prednisone, rituximab ¹ (CVP-R), or Lenalidomide, rituximab ¹
Plasma cell myeloma	Combination chemotherapy (transplant candidates): Bortezomib, dexamethasone, cyclophosphamide, or Bortezomib, dexamethasone, lenalidomide Followed by autologous or mini-allogeneic stem cell transplantation Combination chemotherapy (non-transplant candidates): Bortezomib, lenalidomide, dexamethasone, or Daratumumab, lenalidomide, dexamethasone, or Lenalidomide, dexamethasone, or Bortezomib, cyclophosphamide, dexamethasone
Waldenström macroglobulinemia	Plasmapheresis alone or followed by combination chemotherapy: Ibrutinib with or without rituximab ¹ Bortezomib, dexamethasone, rituximab ¹ , or Cyclophosphamide, dexamethasone, rituximab ¹ , or Bendamustine, rituximab ¹
Polycythemia vera	Phlebotomy or hydroxyurea or aspirin
Non-small cell lung cancer	Combination therapy: Cisplatin, etoposide, or Paclitaxel, carboplatin, or Cisplatin, gemcitabine or docetaxel (squamous histology), or Cisplatin, pemetrexed (nonsquamous histology), or Carboplatin, albumin-bound paclitaxel, or Dabrafenib/trametinib (<i>BRAF</i> V600F mutation), or Carboplatin or cisplatin/pemetrexed/pembrolizumab (nonsquamous); carboplatin/paclitaxel or albumin-bound paclitaxel/pembrolizumab (squamous) Single-agent therapy: Erlotinib, gefitinib, osimertinib, afatinib, or dacomitinib (<i>EGFR</i> mutation positive) Crizotinib, alectinib, ceritinib, or brigatinib (<i>ALK</i> mutation positive) Ceritinib, crizotinib, or entrectinib (<i>ROS1</i> rearrangement) Larotrectinib or entrectinib (<i>NTRK</i> gene fusion positive) Pembrolizumab (PD-L1 ≥ 1%) or atezolizumab (PD-L1 ≥ 50%)
Small cell lung cancer	Combination therapy: Cisplatin, etoposide (limited stage), or Cisplatin, etoposide, durvalumab (extensive stage), or Carboplatin, etoposide, atezolizumab or durvalumab (extensive stage)
Mesothelioma	Combination therapy: Cisplatin or carboplatin/pemetrexed with or without bevacizumab, or Nivolumab/ipilimumab

(continued)

Table 39–2. Treatment choices for cancers responsive to systemic agents. (continued)

Diagnosis	Initial Treatment
Head and neck cancer	Cisplatin with radiation therapy, or Carboplatin with 5-fluorouracil with radiation therapy, or Docetaxel, cisplatin, 5-fluorouracil, or Cisplatin or carboplatin/5-fluorouracil/cetuximab, or Pembrolizumab (PD-L1 ≥ 1%), or Pembrolizumab/cisplatin or carboplatin/5-fluorouracil
Esophageal and esophagogastric junction cancer	Combination therapy: Cisplatin, 5-fluorouracil or capecitabine, or Paclitaxel, carboplatin, or Oxaliplatin, 5-fluorouracil or capecitabine, or 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) Add trastuzumab for <i>HER2</i> -overexpressing metastatic adenocarcinoma
Uterine cancer	Hormone therapy: Progestins, tamoxifen, aromatase inhibitors, or fulvestrant Combination chemotherapy: Carboplatin, paclitaxel Carboplatin, paclitaxel, trastuzumab (<i>HER2</i> positive)
Ovarian cancer	Combination chemotherapy: Paclitaxel, carboplatin, with or without bevacizumab, or 5-Fluorouracil/leucovorin or capecitabine, oxaliplatin
Cervical cancer	With radiation: Cisplatin or carboplatin Combination chemotherapy: Cisplatin or carboplatin, paclitaxel with or without bevacizumab
Breast cancer	Adjuvant hormone therapy: <i>Premenopausal:</i> Tamoxifen <i>Postmenopausal:</i> Aromatase inhibitors (anastrozole, letrozole, exemestane) Adjuvant chemotherapy (<i>HER2</i> negative): Doxorubicin, cyclophosphamide, followed by paclitaxel, or Docetaxel, cyclophosphamide Adjuvant chemotherapy (<i>HER2</i> positive): Doxorubicin, cyclophosphamide, followed by paclitaxel, trastuzumab with or without pertuzumab, or Docetaxel, carboplatin, trastuzumab with or without pertuzumab, or Paclitaxel, trastuzumab
Gestational trophoblastic neoplasia	Single-agent chemotherapy: Methotrexate or dactinomycin for low-risk disease Combination chemotherapy: Etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine (EMA-CO) for high-risk disease
Testicular cancer	Combination chemotherapy: Cisplatin, etoposide (EP), or Bleomycin, etoposide, cisplatin (BEP), or Etoposide, mesna, ifosfamide, cisplatin (VIP)
Kidney (renal cell) cancer	Clear cell histology: Axitinib plus pembrolizumab, ipilimumab plus nivolumab, pazopanib, sunitinib, or cabozantinib Non-clear cell histology: Sunitinib
Bladder cancer	Combination chemotherapy: Gemcitabine, cisplatin, or Methotrexate, vinblastine, doxorubicin, cisplatin (MVAC), or Atezolizumab, or pembrolizumab, or gemcitabine plus carboplatin (cisplatin ineligible)
Prostate cancer	Hormone therapy: Luteinizing hormone-releasing agonist (leuprolide, goserelin, triptorelin, histrelin), or degarelix with or without an antiandrogen (flutamide, bicalutamide, nilutamide, enzalutamide, apalutamide) or abiraterone Chemotherapy: Docetaxel or cabazitaxel or mitoxantrone with corticosteroid
Brain cancer (anaplastic astrocytoma and glioblastoma multiforme)	Single-agent chemotherapy with radiation therapy: Temozolomide
Neuroblastoma	Combination chemotherapy: Cyclophosphamide, doxorubicin, cisplatin, etoposide
Thyroid cancer	Single-agent therapy: Radioiodine (¹³¹ I) or sorafenib, lenvatinib, vandetanib (medullary thyroid cancer) or cabozantinib (medullary thyroid cancer)
Adrenal cancer	Cisplatin or carboplatin with etoposide, with or without doxorubicin, with or without mitotane

(continued)

Table 39–2. Treatment choices for cancers responsive to systemic agents. (continued)

Diagnosis	Initial Treatment
Stomach (gastric) cancer	Combination chemotherapy: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOT) (perioperative) 5-Fluorouracil or capecitabine with oxaliplatin or cisplatin Add trastuzumab for <i>HER2</i> -overexpressing adenocarcinomas
Pancreatic cancer	Combination chemotherapy: Gemcitabine, nab-paclitaxel, or 5-Fluorouracil, leucovorin, irinotecan, oxaliplatin (FOLFIRINOX), or Gemcitabine, capecitabine, or Gemcitabine, cisplatin (for <i>BRCA1/2</i> or <i>PALB2</i> mutation) Single-agent chemotherapy: Gemcitabine
Colon cancer	Combination chemotherapy: 5-Fluorouracil, leucovorin, oxaliplatin (FOLFOX) with or without bevacizumab, or Capecitabine, oxaliplatin (CAPEOX) with or without bevacizumab, or 5-Fluorouracil, leucovorin, irinotecan (FOLFIRI) with or without bevacizumab 5-Fluorouracil, leucovorin, oxaliplatin, irinotecan (FOLFOXIRI) with or without bevacizumab Cetuximab or panitumumab added to FOLFOX or FOLFIRI for <i>KRAS/NRAS/BRAF</i> wild-type and left-sided tumors Capecitabine or 5-fluorouracil/leucovorin with or without bevacizumab Single-agent therapy: Nivolumab or pembrolizumab (deficient mismatch repair [dMMR]/high-level microsatellite instability [MSI-H])
Rectal cancer	5-Fluorouracil or capecitabine or FOLFOX or CAPEOX
Anal cancer	Mitomycin with 5-fluorouracil or capecitabine with radiation Carboplatin, paclitaxel with or without radiation therapy
Carcinoid	Octreotide LAR or lanreotide or everolimus or lutetium Lu 177-dotatate
Osteosarcoma	Combination chemotherapy: Cisplatin, doxorubicin, or Methotrexate, doxorubicin, cisplatin (MAP)
Soft tissue sarcomas	Combination chemotherapy: Doxorubicin, dacarbazine (AD), or Doxorubicin, ifosfamide, mesna (AIM), or Ifosfamide, epirubicin, mesna Single-agent therapy: Imatinib or sunitinib or regorafenib (gastrointestinal stromal tumors) Doxorubicin or epirubicin or liposomal doxorubicin
Melanoma	Pembrolizumab or nivolumab or nivolumab/ipilimumab (non- <i>BRAF</i> mutation) Dabrafenib/trametinib or vemurafenib/cobimetinib or encorafenib/binimatinib (<i>BRAF</i> mutation)
Hepatocellular cancer	Sorafenib or lenvatinib or atezolizumab with bevacizumab
Kaposi sarcoma	Liposomal doxorubicin

¹In patients with past hepatitis B virus (HBV) infection, rituximab should be used with anti-HBV agent (eg, entecavir) prophylaxis since HBV reactivation, fulminant hepatitis, and, rarely, death can occur otherwise.

Table 39–3. Common cancer therapeutic agents.

Chemotherapeutic Agent	Usual Adult Dosage	Adverse Effects
Alkylating Agents—Nitrogen Mustards		
Bendamustine (Treanda)	100–120 mg/m ² intravenously every 3–4 weeks	Acute: hypersensitivity, nausea, vomiting Delayed: myelosuppression, rash, pyrexia, fatigue
Cyclophosphamide (Cytoxan)	500–1000 mg/m ² intravenously every 3 weeks; 100 mg/m ² /day orally for 14 days every 4 weeks; various doses	Acute: nausea and vomiting Delayed: myelosuppression, alopecia, hemorrhagic cystitis, cardiotoxicity (high dose)
Ifosfamide (Ifex)	1200 mg/m ² intravenously daily for 5 days every 3 weeks; various doses	Acute: nausea and vomiting Delayed: alopecia, myelosuppression, hemorrhagic cystitis, neurotoxicity

(continued)

Table 39–3. Common cancer therapeutic agents. (continued)

Chemotherapeutic Agent	Usual Adult Dosage	Adverse Effects
Alkylating Agents—Platinum Analogs		
Carboplatin (Paraplatin)	Area under the curve (AUC)–based dosing use Calvert equation [Dose (mg) = AUC × (GFR + 25)] AUC = 2–7 mg/mL/min every 2–4 weeks	Acute: nausea and vomiting Delayed: myelosuppression, electrolyte disturbances, peripheral neuropathy, nephrotoxicity, hypersensitivity
Cisplatin (Platinol)	50–100 mg/m ² intravenously every 3–4 weeks; 20 mg/m ² /day intravenously for 5 days every 3 weeks; various doses	Acute: nausea and vomiting Delayed: nephrotoxicity, ototoxicity, neurotoxicity, myelosuppression, electrolyte disturbances
Oxaliplatin (Eloxatin)	85–130 mg/m ² intravenously every 2–3 weeks	Acute: peripheral neuropathy exacerbated by cold, nausea, vomiting, diarrhea Delayed: myelosuppression, elevated transaminases
Alkylating Agents—Triazenes		
Dacarbazine (DTIC-Dome)	375 mg/m ² intravenously on days 1 and 15 every 4 weeks; 900–1000 mg/m ² intravenously over 3 to 4 days; various doses	Acute: nausea, vomiting, photosensitivity Delayed: myelosuppression, anorexia, hypotension, flu-like syndrome
Procarbazine (Matulane)	60–100 mg/m ² orally for 14 days every 4 weeks; various doses	Acute: nausea and vomiting Delayed: myelosuppression, disulfiram-like reaction, MAO inhibition, rash
Temozolomide (Temodar)	75 mg/m ² orally daily during radiation for 42 days; 150–200 mg/m ² orally for 5 days every 4 weeks	Acute: nausea, vomiting, constipation Delayed: myelosuppression, fatigue
Antimetabolites—Folate Antagonists		
Methotrexate (MTX; Trexall)	Intrathecal: 12 mg High dose: 1000–12,000 mg/m ² intravenously every 2–3 weeks	Acute: nausea, vomiting, mucositis Delayed: myelosuppression, nephrotoxicity, hepatotoxicity, neurotoxicity, photosensitivity, pulmonary toxicity
Pemetrexed (Alimta)	500 mg/m ² intravenously every 3 weeks	Acute: nausea, vomiting, diarrhea, rash Delayed: myelosuppression, fatigue, mucositis
Antimetabolites—Purine Analogs		
Fludarabine (Fludara)	25 mg/m ² intravenously for 5 days every 4 weeks	Acute: fever, nausea, vomiting Delayed: asthenia, myelosuppression, immunosuppression, neurotoxicity, anorexia
Mercaptopurine (6-MP; Purinethol)	Induction: 2.5–5 mg/kg/day orally Maintenance: 1.5–2.5 mg/kg/day orally	Acute: nausea, vomiting, diarrhea, rash Delayed: myelosuppression, immunosuppression, hepatotoxicity, mucositis
Antimetabolites—Pyrimidine Analogs		
Azacitidine (Vidaza)	75–100 mg/m ² subcutaneously or intravenously for 7 days every 4 weeks	Acute: injection site reaction (subcutaneously), nausea, diarrhea, fever Delayed: myelosuppression, dyspnea, arthralgia
Capecitabine (Xeloda)	1000–1250 mg/m ² orally twice a day for 14 days every 3 weeks	Acute: nausea, vomiting, diarrhea Delayed: hand-foot syndrome, mucositis, hyperbilirubinemia, myelosuppression
Cytarabine (Ara-C, Cytosar U)	Standard dose: 100 mg/m ² /day intravenously via continuous infusion for 7 days High dose: 1000–3000 mg/m ² intravenously every 12 hours for 2–6 days	Acute: nausea, vomiting, rash, flu-like syndrome Delayed: myelosuppression High-dose: neurotoxicity, ocular toxicities
Decitabine (Dacogen)	15 mg/m ² intravenously every 8 hours for 3 days every 8 weeks; 20 mg/m ² intravenously daily for 5 days	Acute: nausea, vomiting, hyperglycemia Delayed: myelosuppression, fever, fatigue, cough
Fluorouracil (Adrucil)	400 mg/m ² intravenous bolus followed by 2400 mg/m ² intravenously over 46 hours every 2 weeks; 1000 mg/m ² intravenously via continuous infusion for 4–5 days every 3–4 weeks; various doses	Acute: nausea, vomiting, diarrhea Delayed: myelosuppression, hand-foot syndrome, mucositis, photosensitivity, cardiotoxicity (rare)

(continued)

Table 39–3. Common cancer therapeutic agents. (continued)

Chemotherapeutic Agent	Usual Adult Dosage	Adverse Effects
Antimetabolites—Pyrimidine Analogs (cont.)		
Gemcitabine (Gemzar)	1000–1250 mg/m ² intravenously on days 1 and 8 every 3 weeks or days 1, 8, 15 every 4 weeks	Acute: nausea, vomiting, rash, flu-like symptoms, fever, diarrhea Delayed: myelosuppression, edema, elevated transaminases
Antimicrotubules—Vinca Alkaloids		
Vinblastine (Velban)	6 mg/m ² intravenously on days 1 and 15 every 4 weeks; various doses	Acute: constipation Delayed: myelosuppression, alopecia, bone pain, malaise
Vincristine (Oncovin)	0.5–1.4 mg/m ² intravenously every 3 weeks; various doses; maximum single dose usually limited to 2 mg	Acute: constipation, nausea Delayed: peripheral neuropathy, alopecia
Antimicrotubules—Taxanes		
Docetaxel (Taxotere)	60–100 mg/m ² intravenously every 3 weeks	Acute: nausea, vomiting, diarrhea, hypersensitivity, rash Delayed: myelosuppression, asthenia, peripheral neuropathy, alopecia, edema, mucositis
Paclitaxel (Taxol)	135–175 mg/m ² intravenously every 3 weeks; 50–80 mg/m ² intravenously weekly; various doses	Acute: diarrhea, nausea, vomiting, hypersensitivity Delayed: myelosuppression, peripheral neuropathy, alopecia, mucositis, arthralgia
Paclitaxel protein-bound (Abraxane)	100–125 mg/m ² on days 1, 8, 15 every 3–4 weeks; 260 mg/m ² intravenously every 3 weeks	Acute: nausea, vomiting, diarrhea Delayed: myelosuppression, peripheral neuropathy, alopecia, asthenia
Enzyme Inhibitors—Anthracyclines		
Daunorubicin (Cerubidine)	30–60 mg/m ² intravenously for 3 days	Acute: nausea, vomiting, diarrhea, red/orange discoloration of urine, infusion-related reactions (liposomal products) Delayed: myelosuppression, mucositis, alopecia, hand-foot syndrome (liposomal doxorubicin), cardiotoxicity (dose related)
Doxorubicin (Adriamycin)	45–75 mg/m ² intravenously every 3 weeks; various doses	
Epirubicin (Ellence)	60–120 mg/m ² intravenously every 3–4 weeks	
Idarubicin (Idamycin)	10–12 mg/m ² intravenously for 3 days	
Liposomal doxorubicin (Doxil, Lipodox)	20–50 mg/m ² intravenously every 3–4 weeks	
Enzyme Inhibitors—Topoisomerase Inhibitors		
Etoposide (Vepesid)	50–100 mg/m ² intravenously for 3–5 days every 3 weeks	Acute: nausea, vomiting, diarrhea, hypersensitivity, fever, hypotension Delayed: myelosuppression, alopecia, fatigue
Irinotecan (Camptosar)	180 mg/m ² intravenously every other week; various doses	Acute: diarrhea, cholinergic syndrome, nausea, vomiting Delayed: myelosuppression, alopecia, asthenia
Targeted Therapy—Monoclonal Antibodies		
Atezolizumab (Tecentriq)	1200 mg intravenously every 3 weeks	Acute: infusion-related reaction Delayed: immune-mediated reactions, fatigue, decreased appetite
Bevacizumab (Avastin)	5–15 mg/kg intravenously every 2–3 weeks	Acute: infusion-related reaction Delayed: hypertension, proteinuria, wound healing complications, gastrointestinal perforation, hemorrhage
Cetuximab (Erbitux)	Loading dose 400 mg/m ² intravenously, maintenance dose 250 mg/m ² intravenously weekly	Acute: infusion-related reaction, nausea, diarrhea Delayed: acneiform skin rash, hypomagnesemia, asthenia, paronychial inflammation, dyspnea
Daratumumab (Darzalex)	16 mg/kg intravenously weekly for weeks 1–8, every 2 weeks for weeks 9–24, and every 4 weeks from week 25 until disease progression	Acute: infusion-related reaction, nausea Delayed: myelosuppression, fatigue, upper respiratory tract infection

(continued)

Table 39–3. Common cancer therapeutic agents. (continued)

Chemotherapeutic Agent	Usual Adult Dosage	Adverse Effects
Targeted Therapy—Monoclonal Antibodies (cont.)		
Ipilimumab (Yervoy)	1–10 mg/kg intravenously every 3 weeks for a total of four doses	Acute: infusion-related reaction Delayed: immune-related reactions, fatigue
Nivolumab (Opdivo)	240 mg intravenously every 2 weeks or 480 mg every 4 weeks	Acute: vomiting Delayed: fatigue, musculoskeletal pain, rash, pruritus, cough, elevated transaminases
Obinutuzumab (Gazyva)	Cycle 1: 100 mg intravenously on day 1, 900 mg on day 2, 1000 mg on days 8 and 15 of a 28-day cycle; cycles 2–6: 1000 mg intravenously on day 1	Acute: infusion-related reaction, tumor lysis syndrome Delayed: myelosuppression, pyrexia, cough, musculoskeletal disorder, potential hepatitis B reactivation
Panitumumab (Vectibix)	6 mg/kg intravenously every 2 weeks	Acute: infusion-related reaction, nausea Delayed: acneiform skin rash, hypomagnesemia, asthenia, paronychia, fatigue, dyspnea
Pembrolizumab (Keytruda)	200 mg intravenously every 3 weeks or 400 mg every 6 weeks	Acute: infusion-related reaction, nausea Delayed: immune-mediated reactions, fatigue, cough
Pertuzumab (Perjeta)	840 mg intravenously once followed by 420 mg intravenously every 3 weeks	Acute: infusion-related reaction, diarrhea, nausea Delayed: fatigue, alopecia, neutropenia, rash, peripheral neuropathy, cardiomyopathy
Rituximab (Rituxan)	375 mg/m ² intravenously weekly for 4 weeks, or every 3–4 weeks	Acute: infusion-related reaction, tumor lysis syndrome Delayed: lymphopenia, asthenia, rash, potential hepatitis B reactivation
Trastuzumab (Herceptin)	Initial dose 4 mg/kg intravenously, then 2 mg/kg intravenously weekly; or initial dose 8 mg/kg, then 6 mg/kg, intravenously every 3 weeks	Acute: headache, nausea, diarrhea, infusion-related reaction Delayed: myelosuppression, pyrexia, cardiomyopathy, pulmonary toxicity (rare)
Targeted Therapy—Kinase Inhibitors		
Acalabrutinib	100 mg orally twice daily	Acute: diarrhea Delayed: myelosuppression, upper respiratory infection, musculoskeletal pain
Afatinib (Gilotrif)	40 mg orally once daily without food	Acute: diarrhea Delayed: acneiform rash, stomatitis, paronychia
Alectinib (Alecensa)	600 mg orally twice daily with food	Acute: none Delayed: myelosuppression, fatigue, edema, myalgia, dyspnea, elevated transaminases
Axitinib (Inlyta)	5–10 mg orally twice daily	Acute: diarrhea, nausea, vomiting Delayed: hypertension, fatigue, dysphonia, hand-foot syndrome, elevated transaminases
Bosutinib (Bosulif)	500–600 mg orally once daily with food	Acute: diarrhea, nausea, vomiting Delayed: myelosuppression, rash, abdominal pain, hepatotoxicity, fluid retention
Ceritinib (Zykadia)	740 mg orally once daily	Acute: diarrhea, nausea, vomiting Delayed: elevated transaminases, abdominal pain, fatigue, decreased appetite
Cobimetinib (Cotellic)	60 mg orally once daily on days 1–21 of a 28-day cycle	Acute: diarrhea, photosensitivity reaction, nausea, vomiting Delayed: myelosuppression, hepatotoxicity, rash, cardiomyopathy (with vemurafenib)
Crizotinib (Xalkori)	250 mg orally twice daily	Acute: nausea, vomiting, diarrhea, constipation Delayed: vision disorder, edema, elevated transaminases, fatigue
Dabrafenib (Tafinlar)	150 mg orally twice daily without food	Acute: headache Delayed: hyperkeratosis, fever, hand-foot syndrome, hyperglycemia, hypophosphatemia
Dacomitinib (Vizimpro)	45 mg orally once daily	Acute: diarrhea Delayed: rash, paronychia, mucositis, cough, interstitial lung disease

(continued)

Table 39–3. Common cancer therapeutic agents. (continued)

Chemotherapeutic Agent	Usual Adult Dosage	Adverse Effects
Targeted Therapy—Kinase Inhibitors (cont.)		
Dasatinib (Sprycel)	100–180 mg orally once daily	Acute: diarrhea, nausea, vomiting Delayed: myelosuppression, fluid retention, fatigue, dyspnea, musculoskeletal pain, rash
Entrectinib (Rozlytrek)	600 mg orally daily	Acute: nausea, vomiting, diarrhea Delayed: fatigue, cognitive impairment, heart failure, potential for birth defects, hepatotoxicity, vision disorder, prolonged QT interval (rare)
Erlotinib (Tarceva)	100 or 150 mg orally once daily without food	Acute: diarrhea, nausea, vomiting Delayed: acneiform skin rash, fatigue, anorexia, dyspnea
Gefitinib (Iressa)	250 mg orally once daily	Acute: diarrhea Delayed: acneiform skin rash
Ibrutinib (Imbruvica)	420 or 560 mg orally once daily	Acute: diarrhea, nausea Delayed: myelosuppression, fatigue, edema, rash, elevated serum creatinine, hemorrhage
Imatinib (Gleevec)	100–800 mg orally once daily with food	Acute: nausea, vomiting, diarrhea Delayed: edema, muscle cramps, rash, myelosuppression, hepatotoxicity
Larotrectinib (Vitrakvi)	100 mg orally twice daily	Acute: nausea, vomiting, diarrhea Delayed: fatigue, cognitive impairment, potential for birth defects, hepatotoxicity
Lenvatinib (Lenvima)	24 mg orally daily	Acute: hypertension, nausea, vomiting, diarrhea Delayed: fatigue, arthralgia/myalgia, stomatitis, hand-foot syndrome
Nilotinib (Tasigna)	300 or 400 mg orally twice daily without food	Acute: nausea, vomiting, diarrhea Delayed: rash, fatigue, myelosuppression, prolonged QT interval (rare)
Osimertinib (Tagrisso)	80 mg orally once daily	Acute: diarrhea Delayed: myelosuppression, rash, dry skin, nail toxicity, cardiomyopathy (rare), QTc interval prolongation (rare)
Pazopanib (Votrient)	800 mg orally once daily without food	Acute: diarrhea, nausea, vomiting Delayed: hypertension, hair color changes, hepatotoxicity, hemorrhage
Regorafenib (Stivarga)	160 mg orally once daily with food (low-fat breakfast)	Acute: diarrhea Delayed: asthenia, hand-foot syndrome, anorexia, hypertension, mucositis, myelosuppression, hepatotoxicity
Sorafenib (Nexavar)	400 mg orally twice daily without food	Acute: diarrhea and nausea Delayed: fatigue, hand-foot syndrome, rash, hypertension, hemorrhage
Sunitinib (Sutent)	50 mg orally once daily for 4 weeks followed by 2 weeks rest; 37.5 mg orally daily	Acute: diarrhea and nausea Delayed: hypertension, hand-foot syndrome, rash, yellow discoloration of skin, fatigue, hypothyroidism, mucositis, left ventricular dysfunction, bleeding, hepatotoxicity
Trametinib (Mekinist)	2 mg orally once daily without food	Acute: rash, diarrhea Delayed: elevated transaminases, lymphedema, cardiomyopathy
Vemurafenib (Zelboraf)	960 mg orally twice daily	Acute: nausea, hypersensitivity (rare) Delayed: photosensitivity, rash, arthralgia, alopecia, fatigue, prolonged QT interval, cutaneous squamous cell carcinoma

(continued)

Table 39–3. Common cancer therapeutic agents. (continued)

Chemotherapeutic Agent	Usual Adult Dosage	Adverse Effects
Miscellaneous Agents		
Abiraterone (Zytiga)	1000 mg orally once daily	Acute: diarrhea, edema Delayed: adrenal insufficiency, hepatotoxicity, joint pain, hypokalemia
Bleomycin (Blenoxane)	10 units/m ² intravenously on days 1 and 15 every 28 days; 30 units intravenously on days 2, 9, and 16 every 21 days	Acute: hypersensitivity, fever Delayed: skin reaction (rash, hyperpigmentation of skin, striae), mucositis, pneumonitis
Bortezomib (Velcade)	1.3 mg/m ² intravenous bolus or subcutaneously on days 1, 4, 8, 11 followed by a 10-day rest, or weekly for 4 weeks followed by 13-day rest	Acute: nausea, vomiting, diarrhea Delayed: peripheral neuropathy, fatigue, myelosuppression
Hydroxyurea (Hydrea)	20–30 mg/kg orally daily	Acute: none Delayed: myelosuppression
Lenalidomide (Revlimid)	5–25 mg orally once daily on days 1–21 of 28-day cycle; or continuously	Acute: diarrhea, rash Delayed: myelosuppression, fatigue, venous thromboembolism, potential for birth defects
Mitomycin (Mutamycin)	10–20 mg/m ² intravenously every 4–8 weeks; 20–40 mg intravesically	Acute: cystitis (intravesically), nausea, vomiting Delayed: myelosuppression, mucositis, anorexia
Pegaspargase (Oncaspar)	2000–2500 international units/m ² intramuscularly every 14 days	Acute: hypersensitivity Delayed: febrile neutropenia, coagulation abnormalities, hepatotoxicity, pancreatitis
Venetoclax (Venclexta)	20 mg orally daily during week 1; 50 mg daily during week 2; 100 mg daily during week 3; 200 mg daily during week 4; then 400 mg orally daily thereafter	Acute: diarrhea, nausea, vomiting, tumor lysis syndrome Delayed: myelosuppression, upper respiratory infections, fatigue
Antiandrogens		
Apalutamide (Erleada)	240 mg orally daily	Acute: fatigue, diarrhea Delayed: arthralgia, hot flashes, falls, peripheral edema, seizure (rare)
Bicalutamide (Casodex)	50 mg orally once daily	Acute: none Delayed: hot flashes, back pain, asthenia
Enzalutamide (Xtandi)	160 mg orally once daily	Acute: asthenia, diarrhea Delayed: hot flashes, arthralgia, peripheral edema, seizure (rare)
Flutamide (Eulexin)	250 mg orally every 8 hours	Acute: diarrhea Delayed: hot flashes, hepatotoxicity
Nilutamide (Nilandron)	300 mg orally for 30 days, then 150 mg orally once daily	Acute: none Delayed: visual disturbances (impaired adaptation to dark), hot flashes, disulfiram-like reaction
Selective Estrogen Receptor Modulators		
Tamoxifen (Nolvadex)	20–40 mg orally once daily	Acute: none Delayed: hot flashes, vaginal discharge, menstrual irregularities, arthralgia
Aromatase Inhibitors		
Anastrozole (Arimidex)	1 mg orally once daily	Acute: nausea Delayed: hot flashes, peripheral edema, asthenia, hypercholesterolemia, arthralgia/myalgia, osteoporosis
Exemestane (Aromasin)	25 mg orally once daily	
Letrozole (Femara)	2.5 mg orally once daily	

(continued)

Table 39–3. Common cancer therapeutic agents. (continued)

Chemotherapeutic Agent	Usual Adult Dosage	Adverse Effects
Pure Estrogen Receptor Antagonist		
Fulvestrant (Faslodex)	500 mg intramuscularly on days 1, 15, 29, then monthly	Acute: injection site reaction, nausea Delayed: hot flashes, bone pain, elevated transaminases
LHRH Analogs		
Goserelin acetate (Zoladex)	3.6 mg subcutaneously every month; 10.8 mg subcutaneously every 3 months	Acute: injection site discomfort Delayed: hot flashes, tumor flare, edema, decreased libido, erectile dysfunction, osteoporosis
Leuprorelin (Lupron)	7.5 mg intramuscularly or subcutaneously every month; 22.5 mg intramuscularly or subcutaneously every 3 months; 30 mg intramuscularly or subcutaneously every 4 months; 45 mg intramuscularly or subcutaneously every 6 months	
Triptorelin pamoate (Trelstar)	3.75 mg intramuscularly every 4 weeks; 11.25 mg intramuscularly every 12 weeks; 22.5 mg intramuscularly every 24 weeks	
LHRH Antagonist		
Degarelix (Firmagon)	240 mg subcutaneously once, then 80 mg subcutaneously every 28 days	Acute: injection site reaction Delayed: hot flashes, weight gain, elevated transaminases, QT prolongation

AV, atrioventricular; GFR, glomerular filtration rate; LHRH, luteinizing hormone-releasing hormone; MAO, monoamine oxidase; MCV, mean corpuscular volume.

TYPES OF CANCER

LUNG CANCER

Sunny Wang, MD

BRONCHOGENIC CARCINOMA



ESSENTIALS OF DIAGNOSIS

- ▶ New cough or change in chronic cough.
- ▶ Dyspnea, hemoptysis, anorexia, weight loss.
- ▶ Enlarging lung nodule or mass; persistent opacity, atelectasis, or pleural effusion on chest radiograph or CT scan.
- ▶ Cytologic or histologic findings of lung cancer in sputum, pleural fluid, or biopsy specimen.

General Considerations

Lung cancer is the leading cause of cancer deaths in both men and women. The American Cancer Society estimates 228,820 new diagnoses and 135,720 deaths from lung cancer in the United States in 2020, accounting for approximately 13% of new cancer diagnoses and 22% of all cancer deaths. More Americans die of lung cancer than of colorectal, breast, and prostate cancers combined.

Cigarette smoking causes 85–90% of cases of lung cancer. The causal connection between cigarettes and lung cancer is established not only epidemiologically but also through identification of carcinogens in tobacco smoke and analysis of the effect of these carcinogens on specific oncogenes expressed in lung cancer.

Other environmental risk factors for the development of lung cancer include exposure to environmental tobacco smoke, radon, asbestos, diesel exhaust, ionizing radiation, metals (arsenic, chromium, nickel, iron oxide), and industrial carcinogens. A familial predisposition to lung cancer is recognized. Certain diseases are associated with an increased risk of lung cancer, including pulmonary fibrosis, chronic obstructive pulmonary disease, and sarcoidosis.

The median age at diagnosis of lung cancer in the United States is 70; it is unusual under the age of 40. The combined relative 5-year survival rate for all stages of lung cancer is currently 21%.

There are five main histologic categories of bronchogenic carcinoma. **Squamous cell carcinomas** (23% of cases, based on US SEER data 2013–2017) arise from the bronchial epithelium and often present as intraluminal masses. They are usually centrally located and can present with hemoptysis. **Adenocarcinomas** (50% of cases) arise from mucous glands or from any epithelial cell within or distal to the terminal bronchioles. They usually present as peripheral nodules or masses. **Adenocarcinomas in situ** (formerly **bronchioloalveolar cell carcinomas**) spread along preexisting alveolar structures (lepidic growth) without evidence of invasion. **Large cell carcinomas** (1.3% of

cases) are a heterogeneous group of undifferentiated cancers that share large cells and do not fit into other categories. Large cell carcinomas are typically aggressive and have rapid doubling times. They present as central or peripheral masses. Cancers that are not better differentiated on pathologic review other than non–small cell carcinomas (NSCLC) or carcinomas not otherwise specified make up about 13% of cases. **Small cell carcinomas** (13% of cases) are tumors of bronchial origin that typically begin centrally, infiltrating submucosally to cause narrowing of the bronchus without a discrete luminal mass. They are aggressive cancers that often involve regional or distant metastasis on presentation.

For purposes of staging and treatment, bronchogenic carcinomas are divided into small cell lung cancer (SCLC) and the other four types, labeled NSCLC. This practical classification reflects different natural histories and different treatment. SCLC is prone to early hematogenous spread and has a more aggressive course with a median survival (untreated) of 6–18 weeks.

► Clinical Findings

Lung cancer is symptomatic at diagnosis in a majority of patients. The clinical presentation depends on the type and location of the primary tumor, the extent of local spread, and the presence of distant metastases and any paraneoplastic syndromes.

A. Symptoms and Signs

Anorexia, weight loss, or asthenia occurs in 55–90% of patients presenting with a new diagnosis of lung cancer. Up to 60% of patients have a new cough or a change in a chronic cough; 6–31% have hemoptysis; and 25–40% complain of pain, either nonspecific chest pain or pain from bony metastases to the vertebrae, ribs, or pelvis. Local spread may cause endobronchial obstruction with atelectasis and postobstructive pneumonia, pleural effusion (12–33%), change in voice (compromise of the recurrent laryngeal nerve), superior vena cava syndrome (obstruction of the superior vena cava with supraclavicular venous engorgement), and Horner syndrome (ipsilateral ptosis, miosis, and anhidrosis from involvement of the inferior cervical ganglion and the paravertebral sympathetic chain). Distant metastases to the liver are associated with asthenia and weight loss. Brain metastases (10% in NSCLC, more common in adenocarcinoma, and 20–30% in SCLC) may present with headache, nausea, vomiting, seizures, dizziness, or altered mental status.

Paraneoplastic syndromes are patterns of organ dysfunction related to immune-mediated or secretory effects of neoplasms. These syndromes occur in 10–20% of lung cancer patients. They may precede, accompany, or follow the diagnosis of lung cancer. In patients with small cell carcinoma, the syndrome of inappropriate antidiuretic hormone (SIADH) can develop in 10–15%; in those with squamous cell carcinoma, hypercalcemia can develop in 10%. Digital clubbing is seen in up to 20% of patients at diagnosis (see Figure 6–42). Other common paraneoplastic syndromes include increased ACTH production, anemia,

hypercoagulability, peripheral neuropathy, and the Lambert–Eaton myasthenic syndrome. Their recognition is important because treatment of the primary tumor may improve or resolve symptoms even when the cancer is not curable.

B. Laboratory Findings

The diagnosis of lung cancer rests on examination of a tissue or cytology specimen. **Sputum cytology** is highly specific but insensitive; the yield is highest when there are lesions in the central airways. While the diagnostic yield of **CT-guided biopsy** of peripheral nodules approaches 80–90%, the rates of pneumothorax are significant (15–30%), especially in those with emphysema. **Thoracentesis** (sensitivity 50–65%) can be used to establish a diagnosis of lung cancer in patients with malignant pleural effusions. Fine-needle aspiration (FNA) of palpable supraclavicular or cervical lymph nodes is frequently diagnostic.

Fiberoptic bronchoscopy allows visualization of the major airways, cytology brushing of visible lesions or lavage of lung segments with cytologic evaluation of specimens, direct biopsy of endobronchial abnormalities, blind transbronchial biopsy of the pulmonary parenchyma or peripheral nodules, and FNA biopsy of mediastinal lymph nodes. The use of fluorescence bronchoscopy improves the ability to identify early endobronchial lesions, and endobronchial and transesophageal endoscopic ultrasound enhance the direction and yield of FNA of mediastinal nodes. Electromagnetic navigational bronchoscopy allows bronchoscopic approaches to small peripheral nodules. Mediastinoscopy, video-assisted thoracoscopic surgery (VATS), and thoracotomy may be necessary in cases where less invasive techniques fail to yield a diagnosis.

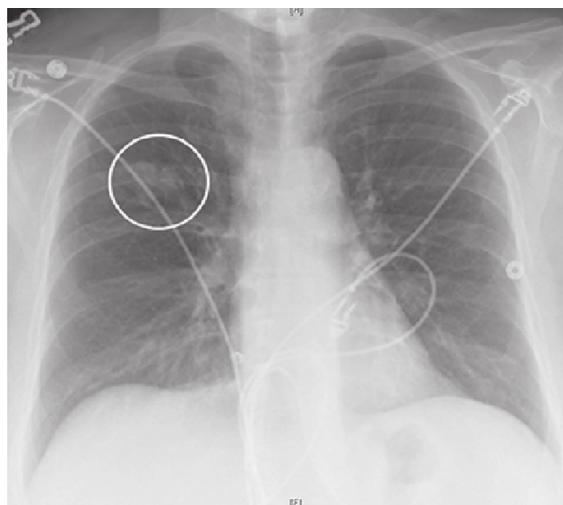
C. Imaging

Nearly all patients with lung cancer have abnormal findings on chest radiography or CT scan (Figure 39–1). These findings are rarely specific for a particular diagnosis. Interpretation of characteristic findings in isolated nodules is described in Chapter 9.

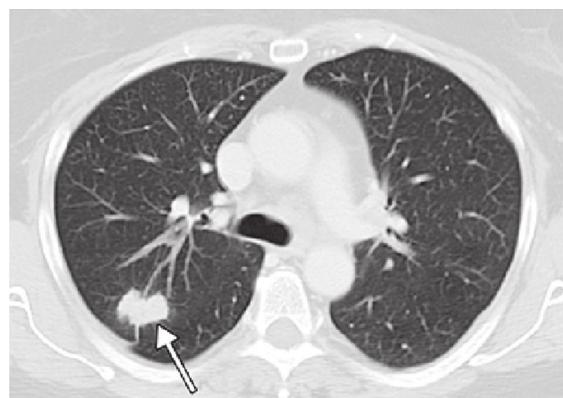
D. Special Examinations

1. Staging—Accurate staging is crucial (1) to provide the clinician with information to guide treatment, (2) to provide the patient with accurate information regarding prognosis, and (3) to standardize entry criteria for clinical trials to allow interpretation of results.

Staging of NSCLC uses two integrated systems and is continuously updated with the eighth edition of the **AJCC/Union for International Cancer Control (UICC)** stage classification for lung cancer in effect since January 2018. The **AJCC TNM international staging system** attempts a physical description of the neoplasm: T describes the size and location of the primary tumor; N describes the presence and location of nodal metastases; and M refers to the presence or absence of distant metastases. These TNM stages are grouped into summary stages I–IV, and these are used to guide therapy. Many patients with stage I and stage II disease are cured through surgery. Patients with stage IIIB and stage IV disease do not benefit from surgery



A



B

Figure 39-1. Squamous cell carcinoma of the right lung on chest radiograph (A) and CT scan (B). (Reproduced, with permission, from Elsayes KM, Oldham SA. *Introduction to Diagnostic Radiology*. McGraw-Hill, 2014.)

(Table 39–4). Patients with stage IIIA disease have locally invasive disease that may benefit from surgery in selected cases as part of multimodality therapy.

SCLC is traditionally divided into two categories: **limited disease** (30%), when the tumor is limited to the unilateral hemithorax (including contralateral mediastinal nodes); or **extensive disease** (70%), when the tumor extends beyond the hemithorax (including pleural effusion). It is also recommended to stage SCLC according to the TNM staging system.

For both SCLC and NSCLC, a complete examination is essential to exclude obvious metastatic disease to lymph nodes, skin, and bone. A detailed history is essential because the patient's performance status is a powerful predictor of disease course. All patients should have measurement of a complete blood count (CBC), serum electrolytes, calcium, creatinine, liver biochemical tests, lactate dehydrogenase, and albumin.

Table 39–4. Five-year survival rates for non–small cell lung cancer, based on TNM staging.

Stage	TNM Subset	5-Year Survival for Clinical TNM	5-Year Survival for Pathologic TNM
0	Carcinoma in situ		
1A1	T1aN0M0	92%	90%
1A2	T1bN0M0	83%	85%
IA3	T1cN0M0	77%	80%
IB	T2aN0M0	68%	73%
IIA	T2bN0M0	60%	65%
IIB	T1/T2, N1M0 T3N0M0	53%	56%
IIIA	T1/T2, N2M0 T3N1M0 T4, N0/N1, M0	36%	41%
IIIB	T1/T2, N3M0 T3/T4, N2M0	26%	24%
IIIC	T3/T4, N3M0	13%	12%
IVA	Any T, Any N, M1a/M1b	10%	—
IVB	Any T, Any N, M1c	0%	—

Data from multiple sources. Modified and reproduced, with permission, from Detterbeck FC et al. The Eighth Edition Lung Cancer Stage Classification. *Chest*. 2017;151:193. Copyright © Elsevier; and data from Goldstraw P et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;11:39.

NSCLC patients being considered for surgery require meticulous evaluation to identify those with resectable disease. CT imaging is key for staging candidates for resection. The sensitivity and specificity of CT imaging for identifying lung cancer metastatic to the mediastinal lymph nodes are 57% (49–66%) and 82% (77–86%), respectively. Therefore, chest CT imaging alone does not provide definitive staging information. CT imaging helps determine where to biopsy, and how the mediastinum should be sampled.

Positron emission tomography (PET) using 2-[¹⁸F]fluoro-2-deoxyglucose (FDG) is an important modality for identifying metastatic foci in the mediastinum or distant sites. The sensitivity and specificity of PET for detecting mediastinal spread of primary lung cancer depend on the size of mediastinal nodes or masses. When mediastinal lymph nodes smaller than 1 cm are present, the sensitivity and specificity of PET for tumor involvement of nodes are 74% and 96%, respectively. When CT shows lymph nodes larger than 1 cm, the sensitivity and specificity are 95% and 76%, respectively.

The combination of PET and CT imaging has improved preoperative staging compared with CT or PET alone. Whole body fusion PET-CT imaging is most useful to

confirm lack of regional or metastatic disease in NSCLC patients who are candidates for surgical resection.

Obtaining an MRI of the brain is important to rule out brain metastases in patients with SCLC and in patients with NSCLC with at least stage II disease or poorly differentiated histologies.

2. Preoperative assessment—See Chapter 3.

3. Pulmonary function testing—Many patients with NSCLC have moderate to severe chronic lung disease that increases the risk of perioperative complications as well as long-term pulmonary insufficiency following lung resection. All patients considered for surgery require spirometry. In the absence of other comorbidities, patients with good lung function (preoperative FEV₁ 2 L or more) are at low risk for complications from lobectomy or pneumonectomy. High-risk patients include those with a predicted postoperative FEV₁ less than 700 mL (or less than 40% of predicted FEV₁).

4. Screening—Screening with low-dose helical CT scans has been shown to improve mortality rates for lung cancer. The National Lung Screening Trial, a multicenter randomized US trial involving over 53,000 current and former heavy smokers, showed that screening annually with low-dose helical CT for 3 years yielded a 20% relative reduction in lung cancer mortality and 6.7% reduction in all-cause mortality compared to chest radiography. Given these findings, US professional organizations have recommended annual screening with low-dose helical CT for lung cancer. The 2021 US Preventive Services Task Force (USPSTF) recommends annual low-dose CT for smokers aged 50–80 who have at least a 20 pack-year smoking history and who either currently smoke or have quit within the last 15 years. Smoking cessation policies and efforts should be integrated with any screening program.

Treatment

A. Non-Small Cell Lung Carcinoma

Surgical resection offers the best chance for cure of NSCLC. Clinical features that preclude complete surgical resection include extrathoracic metastases or a malignant pleural effusion; or tumor involving the heart, pericardium, great vessels, esophagus, recurrent laryngeal or phrenic nerves, trachea, main carina, or contralateral mediastinal lymph nodes. Accordingly, stage I and stage II patients are treated with surgical resection where possible. Stage II and select cases of stage IB are additionally recommended to receive adjuvant chemotherapy. Stage IIIA patients have poor outcomes if treated with resection alone. They should undergo multimodality treatment that includes chemotherapy or radiotherapy, or both. Inoperable stage IIIA and stage IIIB patients treated with concurrent chemotherapy and radiation therapy have improved survival. Stage IV patients are treated with systemic therapy (targeted therapy, chemotherapy, or immunotherapy) or symptom-based palliative therapy, or both.

Surgical approach affects outcome. In 1994, the North American Lung Cancer Study Group conducted a prospective trial of stage IA patients randomized to lobectomy

versus limited resection. They reported a threefold increased rate of local recurrence in the limited resection group ($P = 0.008$) and a trend toward an increase in overall death rate (increase of 30%, $P = 0.08$) and increase in cancer-related death rate (increase of 50%, $P = 0.09$), compared with patients receiving lobectomy. However, for patients who cannot tolerate lobectomy, a sublobar resection (wedge resection or segmentectomy) may be considered.

Patients with clinical stage I primary NSCLC, who are not candidates for surgery because of significant comorbidity or other surgical contraindication, are candidates for stereotactic body radiotherapy. Stereotactic body radiotherapy, which is composed of multiple non-parallel radiation beams that converge, allows the delivery of a relatively large dose of radiation to a small, well-defined target. For clinical stage I NSCLC, 3-year local control rates with stereotactic body radiotherapy exceed 90%, and large meta-analyses of nonrandomized data have shown 2-year survival of 70% and 5-year survival of 40%. Patients with locally advanced disease (stages IIIA and IIIB) who are not surgical candidates have improved survival when treated with concurrent chemotherapy and radiation therapy compared with no therapy, radiation alone, or even sequential chemotherapy and radiation.

Neoadjuvant chemotherapy consists of giving antineoplastic drugs in advance of surgery or radiation therapy. Neoadjuvant therapy can be used in select patients with stage IIIA or stage IIIB disease. Some studies suggest a survival advantage.

Adjuvant chemotherapy consists of administering antineoplastic drugs following surgery or radiation therapy. Cisplatin-containing regimens have been shown to confer an overall survival benefit in at least stage II disease and a subset of stage IB disease where primary tumor size exceeds 4 cm. The Lung Adjuvant Cisplatin Evaluation Collaborative Group, a meta-analysis of the five largest cisplatin-based adjuvant trials, reported a 5% absolute benefit in 5-year overall survival with a cisplatin-containing doublet regimen following surgery ($P = 0.005$) in patients with at least stage II disease.

For stage IIIB and stage IV NSCLC, options for therapy include targeted therapy, cytotoxic chemotherapy, and immunotherapy (checkpoint inhibitors) (Tables 39–2 and 39–3). The approach to therapy is individualized based on molecular profiling and PD-L1 testing. Molecular profiling is offered as next-generation sequencing multi-gene assays. The key driver mutations in lung cancer currently include EGFR, ALK, BRAF, ROS1, NTRK, MET, and RET mutations, but only a minority of all lung cancer cases harbor these mutations. K-ras mutation is more commonly found among smokers. Difficulties in testing may arise when only small fine-needle aspirate biopsies are obtained; to have sufficient tissue for analysis, it is recommended that clinicians obtain core biopsies. PD-L1 expression is a flawed but actively used biomarker to assess possible response to checkpoint inhibitor therapy (specifically, programmed death-1 [PD-1] inhibitors).

Targeted therapy has played a pivotal role in advanced NSCLC (Tables 39–2 and 39–3). Activating EGFR mutations are found in approximately 10–20% of the White

population and 30–48% of the Asian population and are usually found among nonsmokers to light smokers, females, and persons with nonsquamous histologies (particularly adenocarcinomas). For patients with *EGFR* mutations, an *EGFR* tyrosine kinase inhibitor (osimertinib, erlotinib, gefitinib, afatinib, or dacomitinib) rather than platinum-based chemotherapy is the first-line treatment. Response rates with *EGFR* tyrosine kinase inhibitors in patients with *EGFR* mutation are at least 70%, and median overall survival is estimated to be 21–33 months. Osimertinib (a third-generation irreversible *EGFR* tyrosine kinase inhibitor) is recommended as first-line treatment of *EGFR*-mutated lung cancers. Phase 3 data show that osimertinib leads to a longer duration of response, longer progression-free survival, and lower rates of severe adverse events compared to earlier generation *EGFR* tyrosine kinase inhibitors.

Approximately 5% of all patients with NSCLC carry translocations of *ALK* resulting in novel fusion gene products with oncogenic activity. For patients with *ALK*-rearranged lung cancers, *ALK* tyrosine kinase inhibitors (alectinib, ceritinib, crizotinib, brigatinib, and lorlatinib) are recommended therapeutic agents. Alectinib and brigatinib are recommended as first-line agents in *ALK*-rearranged lung cancers with response rates ranging from 74% to 83%. For patients who have developed resistance to either first- or second-generation *ALK* inhibitors, lorlatinib (a third-generation *ALK* and *ROS1* tyrosine kinase inhibitor) has shown a response rate of 47%. Approximately 1–2% of NSCLC harbor *ROS1* rearrangements and they are usually lung adenocarcinomas found among nonsmokers or light smokers. *ROS1*-rearranged lung cancers respond to crizotinib (*ALK*, *cMET*, and *ROS1* tyrosine kinase inhibitor) and entrectinib (multikinase inhibitor, including *ROS-1*) with response rates over 70%. *MET* exon 14 (*METex14*) skipping mutations are found in 3% of lung adenocarcinomas. Capmatinib (*MET* inhibitor) is recommended as first-line treatment for patients with *METex14* skipping mutation. *BRAF* mutations have been found in 2% of NSCLC patients. The combination of dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) has shown response rates of over 60% in patients with *BRAF V600E* mutations. Treatment with larotrectinib (*TRKA/B/C* inhibitor) or entrectinib (multikinase inhibitor, including *TRKA/B/C*) is recommended for patients whose tumors reveal *NTRK 1/2/3* gene fusion. Selpercatinib and pralsetinib (RET inhibitors) are recommended first-line treatments for RET fusion-positive NSCLC. Finally, *K-ras* mutations are found among 30% of patients with adenocarcinomas, are associated with smoking, and indicate a poor prognosis. Early clinical trials are already under way evaluating the role of novel *K-ras* inhibitors, sotorasib (AMG 510) and adagrasib (MRTX849), in treating *K-ras G12C* mutated lung cancers.

Immune checkpoint inhibition using PD-1 or PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab, and durvalumab) has an important role in the treatment of NSCLC (Tables 39–2 and 39–3). Checkpoint inhibitors release T cells from the inhibitory signals they receive from tumor cells via the PD-1 pathway, restoring antitumor immunity. For patients with tumors staining greater than

50% for PDL-1, pembrolizumab outperforms first-line platinum-based chemotherapy, with response rates of 45% vs 28% and median progression-free survival of 10 months vs 6 months. Phase 3 trials have shown improved survival outcomes with adding pembrolizumab to platinum-doublet chemotherapy as first-line therapy for patients with advanced NSCLC regardless of PD-L1 status. If patients received chemotherapy alone as first-line treatment, PD-1 inhibitors are recommended as second-line treatment of NSCLC, regardless of PD-L1 staining intensity. However, significant side effects and toxicity have been reported with checkpoint inhibitors, especially autoimmune manifestations such as hepatitis, thyroiditis, hypophysitis, colitis, pneumonitis, and type 1 diabetes mellitus. Recently, a randomized phase 3 trial has shown improved survival outcomes by adding durvalumab as consolidation therapy post-definitive chemoradiation for stage III NSCLCs.

If no targetable mutations are found and there is inadequate PD-L1 expression on tumor cells, patients are either offered combination immunotherapy with cytotoxic chemotherapy or cytotoxic chemotherapy alone (Table 39–2). Although not curative, chemotherapy has been shown in multiple clinical trials to provide a modest increase in overall survival in patients with stage IIIB and stage IV NSCLC compared with supportive care alone, with the median survival increased from 5 months to a range of 8–12 months and 1-year survival rate of 30–40%. Palliative chemotherapy also leads to improved quality of life and symptom control, with first-line therapy involving a platinum-based regimen.

B. Small Cell Lung Carcinoma

Response rates of SCLC to cisplatin and etoposide (Table 39–2) are excellent with 80–90% response in limited-stage disease (50–60% complete response), and 60–80% response in extensive-stage disease (15–20% complete response). However, remissions tend to be short-lived with a median duration of 6–8 months. Once the disease has recurred, median survival is 3–4 months. Overall 2-year survival is 20–40% in limited-stage disease and 5% in extensive-stage disease (Table 39–5). Modest improvement in survival has been achieved with the addition of a checkpoint inhibitor (atezolizumab or durvalumab) to cisplatin or carboplatin and etoposide therapy in extensive stage disease. Thoracic radiation therapy improves survival in patients with limited SCLC and is given concurrently with chemotherapy. There is a high rate of brain metastasis in patients with SCLC, even following a good response to chemotherapy.

Table 39–5. Median survival for small cell lung carcinoma following treatment.

Stage	Mean 2-Year Survival	Median Survival
Limited	20–40%	15–20 months
Extensive	5%	8–13 months

Data from multiple sources, including Van Meerbeeck JP et al. Small-cell lung cancer. Lancet. 2011;378:1741.

Prophylactic cranial irradiation may be considered for patients with limited-stage disease who respond to chemotherapy and in a subset of patients with extensive-stage disease who have had an excellent response to chemotherapy.

C. Palliative Therapy

Photoresection with the Nd:YAG laser is sometimes performed on central tumors to relieve endobronchial obstruction, improve dyspnea, and control hemoptysis. External beam radiation therapy is also used to control dyspnea, hemoptysis, endobronchial obstruction, pain from bony metastases, obstruction from superior vena cava syndrome, and symptomatic brain metastases. Resection of a *solitary* brain metastasis improves quality of life and survival when combined with radiation therapy if there is no evidence of other metastatic disease. Stereotactic radiation therapy is offered for limited brain metastases. Repeated thoracenteses, pleurodesis, and PleurX catheter tube placement are key interventions for palliation of symptomatic malignant pleural effusions. Pain is very common in advanced disease. Meticulous efforts at pain control are essential (see Chapter 5). In addition to standard oncologic care, early referral to a palliative care specialist is recommended in advanced disease to aid in pain and other symptom management. Such palliative care can modestly improve survival.

► Prognosis

The overall 5-year survival rate for lung cancer is approximately 20%. Predictors of survival include the tumor type (SCLC versus NSCLC), molecular profiling, and stage, and the patient's performance status and weight loss in the prior 6 months. Patients with targetable mutations have better overall survival when compared with those without mutations due to superior efficacy of targeted drug therapy.

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PULMONARY METASTASIS

Pulmonary metastasis results from the spread of an extra-pulmonary malignant tumor through vascular or lymphatic channels or by direct extension. Metastases usually occur via the pulmonary artery and typically present as

multiple nodules or masses on chest radiography. The radiographic differential diagnosis of multiple pulmonary nodules also includes pulmonary arteriovenous malformation, infections (including abscesses, septic emboli, and atypical infections), sarcoidosis, rheumatoid nodules, and granulomatosis with polyangiitis. Metastases to the lungs are found in 20–55% of patients with various metastatic malignancies. Carcinomas of the kidney, breast, rectum, colon, and cervix and malignant melanoma are the most likely primary tumors.

Lymphangitic carcinomatosis denotes diffuse involvement of the pulmonary lymphatic network by primary or metastatic lung cancer, probably a result of extension of tumor from lung capillaries to the lymphatics. **Tumor embolization** from extrapulmonary cancer (renal cell carcinoma, hepatocellular carcinoma, choriocarcinoma) is an uncommon route for tumor spread to the lungs. Metastatic cancer may also present as a malignant pleural effusion.

► Clinical Findings

A. Symptoms and Signs

Symptoms are uncommon but include cough, hemoptysis and, in advanced cases, dyspnea and hypoxemia. Symptoms are more often referable to the site of the primary tumor.

B. Laboratory Findings

The diagnosis of metastatic cancer involving the lungs is usually established by identifying a primary tumor. Appropriate studies should be ordered if there is a suspicion of any primary cancer, such as breast, thyroid, testis, colorectal, or prostate, for which specific treatment is available. If the history, physical examination, and initial studies fail to reveal the site of the primary tumor, attention is better focused on the lung, where tissue samples obtained by bronchoscopy, percutaneous needle biopsy, video-assisted thoracoscopic surgery (VATS), or thoracotomy may establish the histologic diagnosis and suggest the most likely primary cancer. Occasionally, cytologic studies of pleural fluid or pleural biopsy reveals the diagnosis.

C. Imaging

Chest radiographs usually show multiple spherical densities with sharp margins. The lesions are usually bilateral, pleural, or subpleural in location, and more common in lower lung zones. Lymphangitic spread and solitary pulmonary nodule are less common radiographic presentations of pulmonary metastasis. CT imaging of the chest, abdomen, and pelvis may reveal the site of a primary tumor and will help determine feasibility of surgical resection of the metastatic lung tumors. FDG PET-CT scan is helpful in identifying the site of a primary cancer and identifying other areas of extrathoracic metastasis.

► Treatment

Once the diagnosis has been established, management consists of treatment of the primary neoplasm and any pulmonary complications. Surgical resection of a *solitary*

pulmonary nodule is often prudent in the patient with known current or previous extrapulmonary cancer. Local resection of one or more pulmonary metastases is feasible in a few carefully selected patients with various sarcomas and carcinomas (such as testis, colorectal, and kidney). About 15–25% of metastatic solid tumor patients have metastases limited to the lungs and are surgical candidates. Surgical resection should be considered only if (1) the primary tumor is under control, (2) the patient has adequate cardiopulmonary reserve to tolerate resection, (3) all metastatic tumor can be resected, (4) effective nonsurgical approaches are not available, and (5) there is no evidence of extrathoracic metastases that are not controlled. Unfavorable prognostic factors also include shorter disease-free interval from primary tumor treatment to presentation of metastases and a larger number of metastases. Retrospective data from the International Registry of Lung Metastases report an overall 5-year survival rate of 36% and 10-year survival rate of 26% after complete resection of pulmonary metastases. Patients who are not surgical candidates but have solitary or limited metastatic disease to the lungs may be candidates for stereotactic radiotherapy, radioablation, or cryotherapy. For patients with unresectable progressive disease, chemotherapy tailored to the primary tumor can be offered, and diligent attention to palliative care is essential (see Chapter 5).

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MESOTHELIOMA



ESSENTIALS OF DIAGNOSIS

- ▶ Unilateral, nonpleuritic chest pain and dyspnea.
- ▶ Distant (> 20 years earlier) history of exposure to asbestos.
- ▶ Pleural effusion or pleural thickening or both on chest radiographs.
- ▶ Malignant cells in pleural fluid or tissue biopsy.

► General Considerations

Mesotheliomas are primary tumors arising from the surface lining of the pleura (80% of cases) or peritoneum (20% of cases). Numerous studies have confirmed the association of **malignant pleural mesothelioma** with exposure to asbestos. The lifetime risk to asbestos workers of developing malignant pleural mesothelioma is as high as 10%. The latent period between exposure and onset of symptoms ranges from 20 to 40 years. The clinician should inquire about asbestos exposure through mining, milling, manufacturing, shipyard work, insulation, brake linings,

building construction and demolition, roofing materials, and other asbestos products (pipes, textiles, paints, tiles, gaskets, panels).

► Clinical Findings

A. Symptoms and Signs

The average interval between onset of symptoms and diagnosis is 2–3 months; the median age at diagnosis is 72–74 years in Western countries. Symptoms include the insidious onset of shortness of breath, nonpleuritic chest pain, and weight loss. Physical findings include dullness to percussion, diminished breath sounds and, in some cases, digital clubbing.

B. Laboratory Findings

Pleural fluid is exudative and often hemorrhagic. Cytologic tests of pleural fluid are often negative. VATS biopsy is usually necessary to obtain an adequate specimen for histologic diagnosis. The histologic variants of malignant pleural mesothelioma are epithelial (50–60%), sarcomatoid (10%), and biphasic (30–40%). Since distinction from benign inflammatory conditions and metastatic adenocarcinoma may be difficult, immunohistochemical stains are important to confirm the diagnosis.

C. Imaging

Radiographic abnormalities consist of nodular, irregular, unilateral pleural thickening and varying degrees of unilateral pleural effusion. Sixty percent of patients have right-sided disease, while only 5% have bilateral involvement. CT scans demonstrate the extent of pleural involvement. PET-CT is used to help differentiate benign from malignant pleural disease, improve staging accuracy, and identify candidates for aggressive surgical approaches.

► Complications

Malignant pleural mesothelioma progresses rapidly as the tumor spreads along the pleural surface to involve the pericardium, mediastinum, and contralateral pleura. The tumor may eventually extend beyond the thorax to involve abdominal lymph nodes and organs. Progressive pain and dyspnea are characteristic. Local invasion of thoracic structures may cause superior vena cava syndrome, hoarseness, Horner syndrome, arrhythmias, and dysphagia.

► Treatment

Chemotherapy is the mainstay of treatment (Tables 39–2 and 39–3), with cytoreductive surgery included in multimodality treatment only if there is localized disease that is amenable to complete macroscopic surgical resection. The optimal surgical approach is still under debate. For localized disease, surgical options include pleurectomy and decortication (surgical stripping of the pleura and pericardium from apex of the lung to diaphragm) or extrapleural pneumonectomy (a radical surgical procedure involving removal of the ipsilateral lung, parietal and visceral pleura,

pericardium, and most of the hemidiaphragm). Surgical cytoreduction alone is not sufficient, and either chemotherapy or radiation therapy (or both) should be included in a multimodality approach. In advanced unresectable disease, palliative chemotherapy with cisplatin and pemetrexed can achieve response rates of 30–40%, can extend median overall survival to 12 months, and can improve quality of life. Adding bevacizumab (a monoclonal antibody to vascular endothelial growth factor [VEGF]) to cisplatin and pemetrexed has been shown to further improve overall survival. Nivolumab and ipilimumab (checkpoint inhibition therapy) can also be offered as first-line treatment, with improved outcomes among those with nonepithelioid tumors. Drainage of pleural effusions, pleurodesis, radiation therapy, and even surgical resection may offer palliative benefit to some patients.

► Prognosis

Most patients die of respiratory failure and complications of local extension. Median survival time from diagnosis ranges from 7 months to 17 months. Five-year survival is 5–10%. Tumors that are predominantly sarcomatoid are more resistant to therapy and have a worse prognosis, with median survivals less than 1 year. Poor prognostic features include poor performance status, non-epithelioid histology, male gender, nodal involvement, elevated lactate dehydrogenase, high white blood cell count, low hemoglobin, and high platelet count.

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HEPATOBLIBIARY CANCERS

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HEPATOCELLULAR CARCINOMA



ESSENTIALS OF DIAGNOSIS

- Usually a complication of cirrhosis.
- Characteristic CT and MRI features may obviate the need for a confirmatory biopsy.

► General Considerations

Malignant neoplasms of the liver that arise from parenchymal cells are called hepatocellular carcinomas (accounting

for 85% of liver cancers); those that originate in the ductular cells are called cholangiocarcinomas (15% or less). Rare tumors of the liver include angiosarcoma and lymphoma.

Worldwide, hepatocellular carcinomas are the fourth most common cause of cancer-related deaths and the sixth most common in incidence. They are associated with cirrhosis in 85% of cases. In Africa and most of Asia, hepatitis B virus (HBV) infection (including “occult” HBV infection; see Chapter 16) is a major etiologic factor, and a family history of hepatocellular carcinoma increases the risk synergistically. In the United States and other Western countries, incidence rates rose over twofold after 1978, with slowing of the rate increase after 2006 except in men ages 55–64, presumably because of the increasing prevalence of cirrhosis caused by chronic hepatitis C virus (HCV) infection and nonalcoholic fatty liver disease (NAFLD). Rates appear to have plateaued since 2010 because of improved treatment of viral hepatitis. In Western countries, risk factors for hepatocellular carcinoma in patients known to have cirrhosis are male gender, age greater than 55 years (although there has been an increase in the number of younger cases), Hispanic or Asian ethnicity, family history in a first-degree relative, overweight, obesity (especially in early adulthood), alcohol use (especially in combination with obesity), tobacco use, diabetes mellitus, hypothyroidism (in women), a prolonged prothrombin time, a low platelet count, and an elevated serum transferrin saturation. The risk of hepatocellular carcinoma is higher in persons with a viral rather than nonviral cause of cirrhosis and may be increased in persons with autoimmune diseases. Other associations include high levels of HBV replication; HBV genotype C; hepatitis D coinfection; elevated serum ALT levels in persons with chronic hepatitis B (in whom antiviral therapy to suppress HBV replication appears to reduce the risk); HCV genotypes 1b and 3; lack of response to antiviral therapy for HCV infection; hemochromatosis (and possibly the C282Y carrier state); aflatoxin exposure (associated with mutation of the TP53 gene); alpha-1-antiprotease (alpha-1-antitrypsin) deficiency; tyrosinemia; and radiation exposure. In patients with the metabolic syndrome and NAFLD, hepatocellular carcinoma may rarely arise from nonalcoholic steatohepatitis in the absence of cirrhosis. Hepatocellular adenoma may be a precursor for hepatocellular carcinoma (see Chapter 16). Evidence for an association with long-term use of oral contraceptives is inconclusive. Whereas sulfonylurea and insulin use may increase the risk of hepatocellular carcinoma, consumption of coffee, vegetables, white meat, fish, and n-3 polyunsaturated fatty acids; use of aspirin; and use of lipophilic HMG-CoA reductase inhibitors (statins) (eg, atorvastatin, simvastatin) and, in diabetic patients, metformin appear to be protective.

The fibrolamellar variant of hepatocellular carcinoma generally occurs in young women and is characterized by a distinctive histologic picture, absence of risk factors, unique genomic profiles, and indolent course. Vinyl chloride exposure is associated with angiosarcoma of the liver. Hepatoblastoma, the most common malignant liver cancer in infants and young children, rarely occurs in adults.

► Clinical Findings

A. Symptoms and Signs

The presence of a hepatocellular carcinoma may be unsuspected until there is deterioration in the condition of a cirrhotic patient who was formerly stable. Cachexia, weakness, and weight loss are associated symptoms. The sudden appearance of ascites, which may be bloody, suggests portal or hepatic vein thrombosis by cancer or bleeding from a necrotic cancer.

Physical examination may show tender enlargement of the liver, occasionally with a palpable mass. In Africa, the typical presentation in young patients is a rapidly expanding abdominal mass. Auscultation may reveal a bruit over the tumor or a friction rub when the tumor has extended to the surface of the liver.

B. Laboratory Findings

Laboratory tests may reveal leukocytosis, as opposed to the leukopenia that is frequently encountered in cirrhotic patients. Anemia is common, but a normal or elevated hematocrit value may be found in up to one-third of patients owing to elaboration of erythropoietin by the tumor. Sudden and sustained elevation of the serum alkaline phosphatase in a patient who was formerly stable is a common finding. HBsAg is present in a majority of cases in endemic areas, whereas in the United States anti-HCV is found in up to 40% of cases. Serum **alpha-fetoprotein (AFP)** levels are elevated in up to 70% of patients with hepatocellular carcinoma in Western countries (although the sensitivity is lower in Blacks and levels are not elevated in patients with fibrolamellar hepatocellular carcinoma); however, mild elevations (10–200 ng/mL [10–200 mcg/L]) are also often seen in patients with chronic hepatitis. Serum levels of des-gamma-carboxy prothrombin are elevated in up to 90% of patients with hepatocellular carcinoma, but they may also be elevated in patients with vitamin K deficiency, chronic hepatitis, and metastatic cancer. Cytologic study of ascitic fluid rarely reveals malignant cells.

C. Imaging

Multiphasic helical CT and MRI with contrast enhancement are the preferred imaging studies for determining the location and vascularity of the tumor; MRI may be more sensitive than CT, and imaging with gadoteric acid increases sensitivity. Lesions smaller than 1 cm may be difficult to characterize. Based on stringent criteria developed by the American College of Radiology through its Liver Imaging Reporting and Data System, the Organ Procurement and Transplantation Network, and the American Association for the Study of Liver Diseases, arterial phase enhancement of a lesion that is greater than or equal to 1 cm in diameter followed by delayed hypointensity (“washout”) has a 90% specificity for hepatocellular carcinoma. Ultrasonography is less sensitive and more operator dependent but is used to screen for hepatic nodules in high-risk patients. Contrast-enhanced ultrasonography has a sensitivity and specificity approaching those of arterial phase helical CT but, unlike CT and MRI, cannot image the

entire liver during the short duration of the arterial phase and is thus associated with false-positive results. In selected cases, endoscopic ultrasonography (EUS) may be useful. PET is under study and appears to improve detection of extrahepatic metastases.

D. Liver Biopsy and Staging

Liver biopsy is diagnostic, although seeding of the needle tract by cancer is a potential risk (1–3%). For lesions smaller than 1 cm, ultrasonography may be repeated every 3 months followed by further investigation of enlarging lesions. For lesions 1 cm or larger, biopsy can be deferred when characteristic arterial hypervascularity and delayed washout are demonstrated on either multiphasic helical CT or MRI with contrast enhancement (or both) in a patient with cirrhosis or if surgical resection is planned.

The TNM system is the commonly used classification to stage hepatocellular carcinoma. Staging is important not only because it correlates with the patient's long-term survival but also because it is used to determine which patients should receive adjuvant or neoadjuvant therapy.

The Barcelona Clinic Liver Cancer (BCLC) staging system is preferred and includes the Child-Pugh class, tumor stage, and liver function and has the advantage of linking overall stage with preferred treatment modalities and with an estimation of life expectancy.

► Screening & Prevention

Surveillance (screening) for the development of hepatocellular carcinoma is recommended in patients with chronic hepatitis B (beginning as early as age 20 in Africans, age 40 in Asian males or Asians with a family history of hepatocellular carcinoma, and age 50 in others) or cirrhosis caused by HCV, HBV, or alcohol. There is some evidence that screening for hepatocellular carcinoma leads to a survival advantage over clinical diagnosis, but only a minority of cases are detected by screening. The standard screening approach is performing ultrasonography and obtaining serum AFP level every 6 months, although AFP testing has low sensitivity. A serum AFP level of 20 ng/mL (20 mcg/L) is generally the cutoff value that should trigger further evaluation. CT and MRI are considered too expensive for screening. The sensitivity of ultrasonography for detecting early hepatocellular carcinoma is only 63%.

The risk of hepatocellular carcinoma developing in a patient with cirrhosis is 3–5% a year. Among patients with cirrhosis, over 60% of nodules smaller than 2 cm in diameter detected on a screening ultrasonography prove to be hepatocellular carcinoma. Patients with cancers detected by surveillance have a less advanced stage on average and greater likelihood that treatment will prolong survival than those whose cancers were not detected by surveillance. However, controversy persists about whether surveillance reduces cancer-related mortality.

Mass vaccination programs against HBV in developing countries are leading to reduced rates of hepatocellular carcinoma. Successful treatment of hepatitis B and of hepatitis C in patients with cirrhosis also reduces the subsequent risk of hepatocellular carcinoma, and thus

hepatocellular carcinoma is considered a preventable neoplasm. However, hepatocellular carcinoma may still occur after clearance of hepatitis B surface antigen or cure of HCV infection, thereby reducing the benefit of treatment for HBV and HCV infection.

Treatment

Surgical resection of a solitary hepatocellular carcinoma may result in cure if liver function is preserved (Child-Pugh class A or possibly B) and portal vein thrombosis is not present. Laparoscopic liver resection has been performed in selected cases. Treatment of underlying chronic viral hepatitis, adjuvant chemotherapy, and adaptive immunotherapy may lower postsurgical recurrence rates.

Liver transplantation may be appropriate for small unresectable tumors in a patient with advanced cirrhosis, with reported 5-year survival rates of up to 75%. The recurrence-free survival may be better for liver transplantation than for resection in patients with well-compensated cirrhosis and small tumors (one tumor less than 5 cm or three or fewer tumors each less than 3 cm in diameter [Milan criteria]) and in those with expanded (University of California, San Francisco) criteria of one tumor less than or equal to 6.5 cm or three or fewer tumors less than or equal to 4.5 cm (or a combined tumor diameter of 8.5 cm) without vascular invasion. The Extended Toronto criteria include tumor differentiation, cancer-related symptoms, confinement of tumor to the liver, and absence of vascular invasion, without regard to tumor number or size, to determine candidacy for liver transplantation and appear to predict outcomes as well as the Milan criteria. After 6 months on the waiting list, patients with stage 2 hepatocellular carcinoma meeting the Milan criteria are awarded a fixed score of 3 points lower than the median Model for End-Stage Liver Disease (MELD) score for patients transplanted in the area where the candidate is listed (see Chapter 16), thereby increasing their chances of undergoing transplantation. However, orthotopic liver transplantation is often impractical because of donor organ shortage, so living donor liver transplantation may be considered in these cases. Patients with larger tumors (3–5 cm), a serum AFP level of 1000 ng/mL (1000 mcg/L) or higher, or a MELD score of 20 or higher have poor posttransplantation survival. In patients with a serum AFP level greater than 1000 ng/mL (1000 mcg/L), down-staging by locoregional therapy to an AFP level less than 500 ng/mL (500 mcg/L) improves survival following subsequent liver transplantation.

Chemotherapy, hormonal therapy with tamoxifen, and long-acting octreotide have not been shown to prolong life, but transarterial chemoembolization (TACE), TACE with drug-eluting beads, transarterial chemoinfusion (TACI), and transarterial radioembolization (TARE) via the hepatic artery are not only palliative but may also prolong survival in patients with a large or multifocal tumor in the absence of extrahepatic spread. TACI and TARE are suitable for patients with portal vein thrombosis. TARE with yttrium-90 has been shown to result in a longer time to progression than TACE. Microwave ablation, radiofrequency ablation, cryotherapy, or injection of absolute ethanol into tumors smaller than 2 cm may prolong survival in patients who are

not candidates for resection and have tumors that are accessible; these interventions, as well as stereotactic body radiation therapy, may also provide a “bridge” to liver transplantation. Microwave ablation is becoming the preferred approach because it allows shorter treatment times and, like radiofrequency ablation, can be performed after TACE in select cases. Cryoablation may result in slower tumor progression than radiofrequency ablation for tumors that are 3.1–4 cm in diameter. Stereotactic body radiation therapy is also being used to treat unresectable hepatocellular carcinoma and may be effective in treating lesions larger than those treated with ablation techniques.

Sorafenib (an oral multikinase inhibitor of Raf kinase, the VEGF receptor, and the platelet-derived growth factor receptor [and others]) prolongs median survival as well as the time to radiologic progression by 3 months in patients with advanced hepatocellular carcinoma and until recently was the standard care in these patients. Lenvatinib is another oral multikinase inhibitor that is FDA approved for the same indications as sorafenib. However, the combination of atezolizumab, an immune checkpoint inhibitor, and bevacizumab, an antibody to the VEGF receptor, has been shown to be superior to sorafenib and has become standard first-line therapy. Regorafenib is an oral multikinase inhibitor that provides a survival benefit for patients whose disease progresses despite sorafenib therapy, and nivolumab and pembrolizumab are immune checkpoint inhibitors that have been approved for advanced hepatocellular carcinoma. The combination of nivolumab and ipilimumab has been recommended as second-line therapy after failure of sorafenib. Cabozantinib, another multikinase inhibitor, has been approved by the FDA for the treatment of hepatocellular carcinoma after prior treatment with sorafenib, as has ramucirumab, an antibody to the VEGF receptor, which is approved for patients with an AFP level greater than or equal to 400 ng/mL (400 mcg/L) and previous treatment with sorafenib. The modified Response Evaluation Criteria in Solid Tumors (mRECIST) are used to assess treatment response based on tumor shrinkage and viability after locoregional and antiangiogenic treatment. Meticulous efforts at palliative care are essential for patients in whom disease progresses despite treatment or in whom advanced tumors, vascular invasion, or extrahepatic spread are present. Severe pain may develop in such patients due to expansion of the liver capsule by the tumor and requires concerted efforts at pain management, including the use of opioids (see Chapter 5).

Prognosis

In the United States, overall 1- and 5-year survival rates for patients with hepatocellular carcinoma are 23% and 5%, respectively. Five-year survival rates rise to 56% for patients with localized resectable disease (T1, T2, selected T3 and T4; N0; M0) but are virtually nil for those with locally unresectable or advanced disease. In patients with HCV-related hepatocellular carcinoma, the serum AFP level at the time of diagnosis of cancer has been reported to be an independent predictor of mortality. A serum AFP level greater than or equal to 200 ng/mL (200 mcg/L) or increases of greater than 15 ng/mL/month predict worse

outcomes in patients awaiting liver transplantation. In patients who are not eligible for surgery, an elevated serum C-reactive protein level is associated with poor survival. Contrary to traditional opinion, the fibrolamellar variant does not have a better prognosis than conventional hepatocellular carcinoma without cirrhosis.

► When to Refer

All patients with hepatocellular carcinoma should be referred to a specialist.

► When to Admit

- Complications of cirrhosis.
- Severe pain.
- For surgery and other interventions.

Bangaru S et al. Review article: new therapeutic interventions for advanced hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2020;51:78. [PMID: 31747082]

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Fanwani F et al. Surveillance for hepatocellular carcinoma: current best practice and future direction. *Gastroenterology*. 2019;157:54. [PMID: 30986389]

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calcification of the gallbladder (porcelain gallbladder), anomalous pancreaticobiliary ductal junction, high parity in women, and aflatoxin exposure. Genetic factors include *K-ras* and *TP53* mutations. Spread of the cancer—by direct extension into the liver or to the peritoneal surface—may be seen on initial presentation.

Carcinoma of the bile ducts (cholangiocarcinoma) accounts for 10–25% of all hepatobiliary malignancies and 3% of all cancer deaths in the United States. It is more prevalent in persons aged 50–70, with a slight male predominance, and more common in Asia. About 50% arise at the confluence of the hepatic ducts (perihilar, or so-called Klatskin, tumors), and 40% arise in the distal extrahepatic bile duct (the incidence of which has risen since 1990); the remainder are intrahepatic (the incidence of which rose dramatically from the 1970s to the early 2000s). Mortality from intrahepatic cholangiocarcinoma has been increasing. The frequency of carcinoma in persons with a choledochal cyst has been reported to be over 14% at 20 years, and surgical excision is recommended. Most cases of cholangiocarcinoma are sporadic. There is an increased incidence of cholangiocarcinoma in patients with bile duct adenoma; Caroli disease; a biliary-enteric anastomosis; ulcerative colitis, especially those with primary sclerosing cholangitis; biliary cirrhosis; diabetes mellitus; hyperthyroidism; chronic pancreatitis; heavy alcohol consumption; smoking; and past exposure to Thorotrast, a contrast agent. Premalignant lesions of the bile duct include biliary intraepithelial neoplasia and intraductal papillary neoplasia of the biliary system (biliary papillomatosis). Aspirin use and statin use are associated with a reduced risk of cholangiocarcinoma, and in diabetic patients, metformin use is associated with a reduced risk of intrahepatic cholangiocarcinoma. In Southeast Asia, hepatolithiasis, chronic typhoid carriage, and infection of the bile ducts with helminths (*Clonorchis sinensis*, *Opisthorchis viverrini*) are associated with an increased risk of cholangiocarcinoma. Hepatitis C virus (and possibly hepatitis B virus) infection, cirrhosis, HIV infection, nonalcoholic fatty liver disease, diabetes mellitus, obesity, and tobacco smoking are risk factors for intrahepatic cholangiocarcinoma.

The TNM system is the commonly used classification to stage carcinoma of the biliary tract, including gallbladder carcinomas and perihilar and intrahepatic cholangiocarcinomas. Staging is important not only because it correlates with the patient's long-term survival but also because it is used to determine which patients should receive adjuvant or neoadjuvant therapy.

Other staging systems consider the patient's age, performance status, tumor extent and form, perineural invasion, vascular encasement, hepatic lobe atrophy, underlying liver disease, and peritoneal metastasis.

► Clinical Findings

A. Symptoms and Signs

Progressive jaundice is the most common and usually the first sign of obstruction of the extrahepatic biliary system. Pain in the right upper abdomen with radiation into the back is usually present early in the course of gallbladder

CARCINOMA OF THE BILIARY TRACT

ESSENTIALS OF DIAGNOSIS

- ▶ Presents with obstructive jaundice, usually painless, often with dilated biliary tract.
- ▶ Pain is more common in gallbladder carcinoma than cholangiocarcinoma.
- ▶ A dilated gallbladder may be palpable (Courvoisier sign).
- ▶ Diagnosis by cholangiography with biopsy and brushings for cytology.

► General Considerations

Carcinoma of the gallbladder occurs in approximately 2% of all people operated on for biliary tract disease; the incidence, like that of carcinoma of the bile ducts, had been decreasing in the United States but may be increasing again in some Western countries because of lifestyle changes. It is notoriously insidious, and the diagnosis is often made unexpectedly at surgery. Cholelithiasis (often large, symptomatic stones) is usually present. Other risk factors are chronic infection of the gallbladder with *Salmonella typhi*, adenomatous gallbladder polyps over 1 cm in diameter (particularly with hypoechoic foci on EUS), mucosal

carcinoma but occurs later in the course of bile duct carcinoma. Anorexia and weight loss are common and may be associated with fever and chills due to cholangitis. Rarely, hematemesis or melena results from erosion of cancer into a blood vessel (hemobilia). Fistula formation between the biliary system and adjacent organs may also occur. The course is usually one of rapid deterioration, with death occurring within a few months.

Physical examination reveals profound jaundice. Pruritus and skin excoriations are common. A palpable gallbladder with obstructive jaundice usually is said to signify malignant disease (Courvoisier sign); however, this clinical generalization has been proven to be accurate only about 50% of the time. Hepatomegaly due to hypertrophy of the unobstructed liver lobe is usually present and is associated with liver tenderness. Ascites may occur with peritoneal implants.

B. Laboratory Findings

With biliary obstruction, laboratory examination reveals predominantly conjugated hyperbilirubinemia, with total serum bilirubin values ranging from 5 to 30 mg/dL. There is usually concomitant elevation of the alkaline phosphatase and serum cholesterol. AST is normal or minimally elevated. The serum CA 19-9 level is elevated in up to 85% of patients and may help distinguish cholangiocarcinoma from a benign biliary stricture (in the absence of cholangitis), but this test is neither sensitive nor specific.

C. Imaging

Ultrasonography and contrast-enhanced, triple-phase, helical CT may show a gallbladder mass in gallbladder carcinoma and intrahepatic mass or biliary dilatation in carcinoma of the bile ducts. CT may also show involved regional lymph nodes and atrophy of a hepatic lobe because of vascular encasement with compensatory hypertrophy of the unaffected lobe. MRI with magnetic resonance cholangiopancreatography (MRCP) and gadolinium enhancement permits visualization of the entire biliary tract and detection of vascular invasion and obviates the need for angiography and, in some cases, direct cholangiography; it is the imaging procedure of choice but may understage malignant hilar strictures. The sensitivity and image quality can be increased with use of ferumoxide enhancement. The features of intrahepatic cholangiocarcinoma on MRI appear to differ from those of hepatocellular carcinoma, with contrast washout in the latter but not the former. In indeterminate cases, PET can detect cholangiocarcinomas as small as 1 cm and lymph node and distant metastases, but false-positive results occur. The most helpful diagnostic studies before surgery are either endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography with biopsy and cytologic specimens, although false-negative biopsy and cytology results are common. Digital image analysis and fluorescent *in situ* hybridization of cytologic specimens for polysomy improve sensitivity. EUS with FNA of tumors, peroral cholangioscopy, confocal laser endomicroscopy, and intraductal ultrasonography may confirm a diagnosis of cholangiocarcinoma in a patient with bile duct stricture and an otherwise indeterminate evaluation, but FNA can result in cancer

seeding and should be avoided if the cancer is potentially resectable.

Treatment

In young and fit patients, curative surgery for gallbladder carcinoma may be attempted if the cancer is well localized. The 5-year survival rate for carcinoma of the gallbladder invading the lamina propria or muscularis (stage 1, T1a or 1b, N0, M0) is as high as 85% with laparoscopic cholecystectomy but drops to 60%, even with a more extended open resection, if there is perimuscular invasion (T2). The role of radical surgery for T3 and T4 tumors is debatable. If the cancer is unresectable at laparotomy, biliary-enteric bypass (eg, Roux-en-Y hepaticojejunostomy) can be performed. Carcinoma of the bile ducts is curable by surgery in less than 10% of cases. If resection margins are negative, the 5-year survival rate may be as high as 47% for intrahepatic cholangiocarcinomas, 41% for hilar cholangiocarcinoma, and 37% for distal cholangiocarcinomas, but the perioperative mortality rate may be as high as 10%. Factors predicting shorter survival for intrahepatic cholangiocarcinoma include large cancer size, multiple cancers, lymph node metastasis, and vascular invasion. Adjuvant chemotherapy with capecitabine has been shown to result in superior overall survival compared with no adjuvant therapy. Palliation can be achieved by placement of a self-expandable metal stent via an endoscopic or percutaneous transhepatic route. Covered metal stents may be more cost-effective than uncovered metal stents because of a longer duration of patency. However, they are associated with a higher rate of stent migration and cholecystitis due to occlusion of the cystic duct and are not associated with longer survival. For perihilar cancers, insertion of a unilateral stent rather than bilateral stents may suffice. Plastic stents are less expensive initially, but not in the long term, because they are more prone to occlude than metal ones; they may be considered in patients expected to survive only a few months. Photodynamic therapy in combination with stent placement prolongs survival when compared with stent placement alone in patients with nonresectable cholangiocarcinoma. Endoscopic retrograde cholangiopancreatography (ERCP)-directed radiofrequency ablation, TACE, and TARE are additional emerging options. Radiotherapy may relieve pain and contribute to biliary decompression. There is limited response to chemotherapy with gemcitabine alone, but the combination of cisplatin and gemcitabine or capecitabine and gemcitabine prolongs survival in patients with locally advanced or metastatic cholangiocarcinoma. Few patients survive for more than 24 months. Although cholangiocarcinoma is generally considered to be a contraindication to liver transplantation because of rapid cancer recurrence, a 5-year survival rate of 75% has been reported in patients with stage I and II perihilar cholangiocarcinoma undergoing chemoradiation and exploratory laparotomy followed by liver transplantation, and a 5-year survival rate of 67% has been reported in those with intrahepatic cholangiocarcinoma.

For those patients whose disease progresses despite treatment, meticulous efforts at palliative care are essential (see Chapter 5).

► When to Refer

All patients with carcinoma of the biliary tract should be referred to a specialist.

► When to Admit

- Biliary obstruction.
- Cholangitis.

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Lauv S et al. Effect of statins on the risk of extrahepatic cholangiocarcinoma. *Hepatology*. 2020;72:1298. [PMID: 32119126]

CARCINOMA OF THE PANCREAS & AMPULLA OF VATER



ESSENTIALS OF DIAGNOSIS

- ▶ Obstructive jaundice (may be painless).
- ▶ Enlarged gallbladder (may be painful).
- ▶ Upper abdominal pain with radiation to back, weight loss, and thrombophlebitis are usually late manifestations.

► General Considerations

Carcinoma is the most common neoplasm of the pancreas. About 75% are in the head and 25% in the body and tail of the organ. Pancreatic carcinomas account for 2% of all cancers and 5% of cancer deaths. Ampullary carcinomas are much less common. Risk factors for pancreatic cancer include age, tobacco use (which is thought to cause 20–25% of cases), heavy alcohol use, obesity, chronic pancreatitis, diabetes mellitus, prior abdominal radiation, family history, and possibly gastric ulcer and exposure to arsenic and cadmium. New-onset diabetes mellitus after age 45 years occasionally heralds the onset of pancreatic cancer. In diabetic patients, metformin use and possibly aspirin use may reduce the risk of pancreatic cancer slightly, but insulin use and glucagon-like peptide-1-based therapy (eg, sitagliptin) may increase the risk. About 7% of patients with pancreatic cancer have a family history of pancreatic cancer in a first-degree relative, compared with 0.6% of control subjects. The majority of pancreatic cancers originate from pancreatic intraepithelial neoplasias, which measure less than 5 mm in diameter and can only be seen with a microscope.

In 5–10% of cases, pancreatic cancer occurs as part of a hereditary syndrome, including familial breast cancer (carriers of *BRCA2* have a 7% lifetime risk of pancreatic cancer), hereditary pancreatitis (*PSS1* mutation), familial

atypical multiple mole melanoma (*p16/CDKN2A* mutation), Peutz-Jeghers syndrome (*STK11/LKB1* mutation), ataxia-telangiectasia (*ATM* mutation), and Lynch syndrome (hereditary nonpolyposis colorectal cancer [*MLH1*, *MSH2*, *MSH6* mutations]).

Neuroendocrine tumors account for 1–2% of pancreatic neoplasms and may be functional (producing gastrin, insulin, glucagon, vasoactive intestinal peptide, somatostatin, growth hormone-releasing hormone, adrenocorticotrophic hormone, and others) or nonfunctional. Cystic neoplasms account for only 1% of pancreatic cancers, but they are important because pancreatic cysts are common and may be mistaken for pseudocysts. A cystic neoplasm should be suspected when a cystic lesion in the pancreas is found in the absence of a history of pancreatitis. At least 15% of all pancreatic cysts are neoplasms. Serous cystadenomas (which account for 32–39% of cystic pancreatic neoplasms and also occur in patients with von Hippel-Lindau disease) are benign. However, mucinous cystic neoplasms (defined by the presence of ovarian stroma and accounting for 10–45% of cystic pancreatic neoplasms), intraductal papillary mucinous neoplasms (21–33% of cystic pancreatic neoplasms), solid pseudopapillary tumors (less than 5%, primarily in young women), and cystic islet cell tumors (3–5%) may be malignant. Their prognoses are better than the prognosis of pancreatic adenocarcinoma, unless the cystic neoplasm is at least locally advanced. Mucinous cystic neoplasms and intraductal papillary mucinous neoplasms account for 15–30% of pancreatic cancers.

► Clinical Findings

A. Symptoms and Signs

Pain is present in over 70% of cases and is often vague, diffuse, and located in the epigastrium or, when the lesion is in the tail, located in the left upper quadrant of the abdomen. Radiation of pain into the back is common and sometimes predominates. Sitting up and leaning forward may afford some relief, and this usually indicates that the lesion has spread beyond the pancreas and is inoperable. Diarrhea, perhaps due to maldigestion, is an occasional early symptom. Migratory thrombophlebitis is a rare sign. Weight loss is a common but late finding and may be associated with depression. Hyperglycemia and decreases in subcutaneous abdominal fat and serum lipid levels have been reported to precede a diagnosis of pancreatic cancer. Occasional patients (often aged 40 years or older) present with acute pancreatitis in the absence of an alternative cause. Jaundice is usually due to biliary obstruction by a cancer in the pancreatic head. A palpable gallbladder is also indicative of obstruction by a neoplasm (Courvoisier sign), but there are frequent exceptions. A hard, fixed, occasionally tender mass may be present. In advanced cases, a hard periumbilical (Sister Mary Joseph's) nodule may be palpable.

B. Laboratory Findings

There may be mild anemia. Glycosuria, hyperglycemia, and impaired glucose tolerance or true diabetes mellitus are found in 10–20% of cases. The serum amylase or lipase

level is occasionally elevated. Liver biochemical tests may suggest obstructive jaundice. Steatorrhea in the absence of jaundice is uncommon. Occult blood in the stool is suggestive of carcinoma of the ampulla of Vater (the combination of biliary obstruction and bleeding may give the stools a distinctive silver appearance). CA 19-9, with a sensitivity of 70% and a specificity of 87%, has not proven useful for early detection of pancreatic cancer; increased values are also found in acute and chronic pancreatitis and cholangitis. Plasma chromogranin A levels are elevated in 88–100% of patients with pancreatic neuroendocrine tumors (NETs).

C. Imaging

Multiphase thin-cut helical CT is generally the initial diagnostic procedure and detects a mass in over 80% of cases. CT identifies metastases, delineates the extent of the tumor, and allows percutaneous FNA for cytologic studies and tumor markers. MRI is an alternative to CT. Ultrasoundography is not reliable because of interference by intestinal gas. PET is a sensitive technique for detecting pancreatic cancer and metastases, but PET-CT is not a routine staging procedure. Selective celiac and superior mesenteric arteriography may demonstrate vessel invasion by cancer, a finding that would preclude attempts at surgical resection, but it is used uncommonly since the advent of multiphase helical CT. EUS is more sensitive than CT for detecting pancreatic cancer and is equivalent to CT for determining nodal involvement and resectability; contrast-enhanced EUS improves accuracy. A normal EUS excludes pancreatic cancer. EUS may also be used to guide FNA or biopsy for tissue diagnosis, tumor markers, and DNA analysis. ERCP may clarify an ambiguous CT or MRI study by delineating the pancreatic duct system or confirming an ampullary or biliary neoplasm. MRCP appears to be at least as sensitive as ERCP in diagnosing pancreatic cancer. In some centers, pancreatoscopy or intraductal ultrasonography is used to evaluate filling defects in the pancreatic duct and assess resectability of intraductal papillary mucinous cancers. With obstruction of the splenic vein, splenomegaly or gastric varices are present, the latter detected by endoscopy, EUS, or angiography.

Cystic neoplasms can be distinguished by their appearance on CT, EUS, and ERCP and features of the cyst fluid on gross, cytologic, and genetic analysis. For example, serous cystadenomas may have a central scar or honeycomb appearance; mucinous cystadenomas are unilocular or multilocular and contain mucin-rich fluid with high carcinoembryonic antigen levels (greater than 200 ng/mL [200 mcg/L]) and *K-ras* mutations; and intraductal papillary mucinous neoplasms are associated with a dilated pancreatic duct and extrusion of gelatinous material from the ampulla.

► Staging

The TNM system is the commonly used classification to stage pancreatic cancer. Staging is important not only because it correlates with the patient's long-term survival but also because it is used to determine which patients should receive adjuvant or neoadjuvant therapy.

► Treatment

Abdominal exploration is usually necessary when cytologic diagnosis cannot be made or if resection is to be attempted (in up to 30% of patients with pancreatic carcinoma). In a patient with a localized mass in the head of the pancreas and without jaundice, laparoscopy may detect tiny peritoneal or liver metastases and thereby avoid resection in 4–13% of patients. Radical pancreaticoduodenal (Whipple) resection is indicated for cancers strictly limited to the head of the pancreas, periampullary area, and duodenum (T1, N0, M0). Five-year survival rates are 20–25% in this group and as high as 40% in those with negative resection margins and without lymph node involvement. Preoperative endoscopic decompression of an obstructed bile duct is often achieved with a plastic stent or short metal stent but does not reduce operative mortality and is associated with complications.

The best surgical results are achieved at centers that specialize in the multidisciplinary treatment of pancreatic cancer. Adjuvant chemotherapy with gemcitabine, 5-fluorouracil, or gemcitabine with capecitabine is superior to no adjuvant therapy. Gemcitabine with capecitabine and a modified FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) regimen have been found to be superior to gemcitabine alone. The role of adjuvant chemoradiation is controversial but often used in the United States. Neoadjuvant chemotherapy with or without radiation is increasingly being used to downstage patients and in those with resectable cancer. Common chemotherapy regimens for this purpose include FOLFIRINOX and gemcitabine with nanoparticle albumin-bound (nab)-paclitaxel. Chemoradiotherapy downstages about 30% of patients with locally advanced disease to allow resection.

When resection is not feasible, endoscopic stenting of the bile duct is performed to relieve jaundice. A plastic stent is generally placed if the patient's anticipated survival is less than 6 months (or if surgery is planned). A metal stent is preferred when anticipated survival is 6 months or greater. Whether covered metal stents designed to prevent cancer ingrowth offer an advantage over uncovered stents is uncertain because covered stents are associated with higher rates of migration and acute cholecystitis due to occlusion of the cystic duct. Surgical biliary bypass may be considered in patients expected to survive at least 6 months. Surgical duodenal bypass may be considered in patients in whom duodenal obstruction is expected to develop; alternatively, endoscopic placement of a self-expandable duodenal stent may be feasible. Chemoradiation may be used for palliation of unresectable cancer confined to the pancreas.

Chemotherapy has been disappointing in metastatic pancreatic cancer, although improved response rates have been reported with FOLFIRINOX and with the combination of gemcitabine and nab-paclitaxel. In patients who have received prior chemotherapy, a regimen of 5-fluorouracil and leucovorin in combination with nanoliposomal irinotecan has resulted in improved survival compared with 5-fluorouracil and leucovorin alone. Celiac plexus nerve block (under CT or endoscopic ultrasound guidance) or thoracoscopic splanchnicectomy may improve pain control.

Surgical resection is the treatment of choice for NETs, when feasible. Lesions that are less than 1 cm in diameter and nonfunctioning without evidence of local invasion or metastasis may be followed expectantly. Metastatic disease may be controlled with long-acting somatostatin analogs, interferon, chemotherapy, peptide-receptor radionuclide therapy, and chemoembolization.

There is a consensus that asymptomatic incidental pancreatic cysts 2 cm or smaller are at low risk for harboring invasive carcinoma. The cysts may be monitored by imaging tests (MRI) in 1 year and then every 2 years for 5 years and probably longer if no changes are observed, with EUS and FNA performed if a cyst enlarges to 3 cm and another high-risk feature (dilated main pancreatic duct, presence of a solid component) develops. The optimal approach is uncertain, however, and other guidelines have been proposed. Surgical resection is indicated for mucinous cystic neoplasms, symptomatic serous cystadenomas, solid pseudopapillary tumors (which have a 15% risk of malignant transformation), and cystic tumors larger than 2 cm in diameter that remain undefined after helical CT, EUS, and diagnostic aspiration. All intraductal papillary mucinous neoplasms of the main pancreatic duct should be resected, but those of branch ducts may be monitored with serial imaging if they (1) are asymptomatic and exhibit benign features; (2) have a diameter less than 3 cm (some authorities recommend a diameter of 1.5 cm or smaller, but even lesions 3 cm or larger may be monitored in elderly persons with no other worrisome cyst features); and (3) lack non-enhancing mural nodules, or thick wall, or abrupt change in the caliber of the pancreatic duct with distal pancreatic atrophy, or possibly bile duct dilatation and gallbladder adenomyomatosis. Most lesions with such benign features remain stable on follow-up, but a risk of malignancy persists for more than 10 years. Moreover, the risk of pancreatic ductal carcinoma and of nonpancreatic cancers is also increased in this group of patients. In the absence of locally advanced disease, survival is higher for malignant cystic neoplasms than for adenocarcinomas. The role of EUS-guided ablative treatment of potentially premalignant pancreatic cysts is under study. Endoscopic resection or ablation, with temporary placement of a pancreatic duct stent, may be feasible for ampullary adenomas, but patients must be followed for recurrence.

► Prognosis

Carcinoma of the pancreas, especially in the body or tail, has a poor prognosis; 80–85% of patients present with advanced unresectable disease, and reported 5-year survival rates range from 2% to 5%. From 1980 to 2010, mortality from pancreatic cancer did not decrease, but it has since started to improve. Obesity may adversely affect mortality in Western countries. Metformin may improve survival in diabetic patients with pancreatic adenocarcinoma, and use of statins preceding a diagnosis of pancreatic cancer may improve survival. Tumors of the ampulla have a better prognosis, with reported 5-year survival rates of 20–40% after resection; jaundice and lymph node involvement are adverse prognostic factors. In carefully selected patients, resection of cancer of the pancreatic head

is feasible and results in reasonable survival. In persons with a family history of pancreatic cancer in at least two first-degree relatives, or with a genetic syndrome associated with an increased risk of pancreatic cancer, screening with EUS and helical CT or MRI/MRCP should be considered beginning at age 50 (age 40 in *CKDN2A* or *PRSS1* mutation carriers and age 35 in those with Peutz-Jeghers syndrome) or 10 years before the age at which pancreatic cancer was first diagnosed in a family member.

For those patients whose disease progresses despite treatment, meticulous efforts at palliative care are essential (see Chapter 5).

► When to Refer

All patients with carcinoma involving the pancreas and the ampulla of Vater should be referred to a specialist.

► When to Admit

Patients who require surgery and other interventions should be hospitalized.

Aslanian HR et al. AGA Clinical Practice Update on pancreas cancer screening in high-risk individuals: expert review. *Gastroenterology*. 2020;159:358. [PMID: 32416142]

Elta GH et al. ACG Clinical Guideline: diagnosis and management of pancreatic cysts. *Am J Gastroenterol*. 2018;113:464. [PMID: 29485131]

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ALIMENTARY TRACT CANCERS

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ESOPHAGEAL CANCER



ESSENTIALS OF DIAGNOSIS

- Progressive dysphagia to solid food.
- Weight loss common.
- Endoscopy with biopsy establishes diagnosis.

► General Considerations

Esophageal cancer usually develops in persons between 50 and 70 years of age. There were an estimated 18,440 new cases of esophageal cancer in the United States in 2020. The overall ratio of men to women is 3:1. There are two histologic types: squamous cell carcinoma and adenocarcinoma, and their incidence has significant geographic variation. Squamous cell carcinoma is associated with smoking, alcohol, poor nutritional status, and drinking hot beverages. It accounts for over 90% of cases of esophageal cancer in

Eastern and Southeast Asia and sub-Saharan Africa. Adenocarcinoma is associated with obesity and gastroesophageal reflux disease, with the majority of cases developing as a complication of Barrett metaplasia due to chronic gastroesophageal reflux. Adenocarcinomas make up the majority of new cases of esophageal cancer in North America and Northern and Western Europe.

► Clinical Findings

A. Symptoms and Signs

The majority (50–60%) of patients with esophageal cancer present with advanced, incurable disease. While early symptoms are nonspecific and subtle, over 90% eventually have solid food dysphagia, which progresses over weeks to months. Odynophagia is sometimes present. Significant weight loss is common. Local tumor extension into the tracheobronchial tree may result in a tracheo-esophageal fistula, characterized by coughing on swallowing or by pneumonia. Chest or back pain suggests mediastinal extension. Recurrent laryngeal nerve involvement may produce hoarseness. Physical examination is often unrevealing. The presence of supraclavicular or cervical lymphadenopathy or of hepatomegaly implies metastatic disease.

B. Laboratory Findings

Laboratory findings are nonspecific. Anemia related to chronic disease or occult blood loss is common. Elevated aminotransferase or alkaline phosphatase concentrations suggest hepatic or bony metastases. Hypoalbuminemia may result from malnutrition.

C. Imaging

A barium esophagogram may be the first study obtained to evaluate dysphagia. The appearance of a polypoid, obstructive, or ulcerative lesion is suggestive of carcinoma and requires endoscopic evaluation. However, even lesions believed to be benign by radiography warrant endoscopic evaluation. Chest radiographs may show adenopathy, a widened mediastinum, pulmonary or bony metastases, or signs of tracheo-esophageal fistula such as pneumonia.

D. Upper Endoscopy

Endoscopy with biopsy establishes the diagnosis of esophageal carcinoma with a high degree of reliability. In some cases, significant submucosal spread of the tumor may yield nondiagnostic mucosal biopsies. Repeat biopsy may be necessary.

► Staging

After confirmation of the diagnosis of esophageal carcinoma, the stage of the disease should be determined since doing so influences the choice of therapy. Patients should undergo evaluation with contrast CT of the chest and abdomen to look for evidence of pulmonary or hepatic metastases, lymphadenopathy, and local tumor extension. If there is no evidence of distant metastases or extensive local spread on CT, then EUS with guided FNA biopsy of suspicious lymph nodes should be performed to evaluate

the locoregional stage. EUS is superior to CT in demonstrating the level of local mediastinal extension and local lymph node involvement. PET with fluorodeoxyglucose or integrated PET-CT imaging is indicated to look for regional or distant spread in patients thought to have localized disease after other diagnostic studies, prior to invasive surgery. Bronchoscopy is sometimes required in esophageal cancers above the carina to exclude tracheobronchial extension. Laparoscopy to exclude occult peritoneal carcinomatosis should be considered in patients with tumors at or near the gastroesophageal junction (see Gastric Adenocarcinoma).

► Differential Diagnosis

Esophageal carcinoma must be distinguished from other causes of progressive dysphagia, including peptic stricture, achalasia, and adenocarcinoma of the gastric cardia with esophageal involvement. Benign-appearing peptic strictures should be biopsied at presentation to exclude occult malignancy.

► Treatment

The approach to esophageal cancer depends on the tumor stage, tumor location, patient preference and functional status, and the expertise of the gastroenterologists, surgeons, oncologists, and radiation oncologists. It is helpful to classify patients into two general categories: those with early stage (curable) disease and those with advanced stage (incurable) disease.

A. Therapy for “Curable” Disease

Superficial esophageal cancers confined to the epithelium (high-grade dysplasia or carcinoma in situ [Tis]), lamina propria (T1a), or submucosal (T1b) are increasingly recognized in endoscopic screening and surveillance programs. Esophagectomy achieves high cure rates for superficial tumors but is associated with mortality (2%) and morbidity. If performed by experienced clinicians, endoscopic mucosal resection of Tis and T1a cancers achieves equivalent long-term survival with less morbidity (see Barrett Esophagus, Chapter 15). Esophagectomy is recommended for superficial tumors that are invasive to the submucosa (T1b) because of higher rates of lymph node metastasis.

1. Surgery with or without neoadjuvant chemoradiation therapy

There are multiple surgical approaches to the resection of invasive but potentially “curable” esophageal cancers (stage Ib, II, IIIA, or IIIB). Accepted techniques include en bloc transthoracic excision of the esophagus with extended lymph node dissection, transhiatal esophagectomy (entailing laparotomy with cervical anastomosis), and minimally invasive esophagectomy techniques. Meta-analysis data suggest equivalent oncologic outcomes from minimally invasive esophagectomy and conventional open techniques, although there are fewer postoperative complications and shorter hospital stays with the laparoscopic approach. Multiple meta-analyses have shown that regardless of surgery type, surgery at a high-volume hospital is associated with decreased perioperative mortality.

Patients with stage I tumors have high cure rates with surgery alone and do not require radiation or chemotherapy. Whether radiation or chemotherapy or both are required in addition to surgery for T2N0 stage II tumors is a subject of ongoing debate. If regional lymph node metastases have occurred (stages IIB and III), the rate of cure with surgery alone is reduced to less than 20%. Meta-analysis of trials comparing neoadjuvant (preoperative) therapy followed by surgery with surgery alone suggests a 13% absolute improvement in 2-year survival with combined therapy. Preoperative (neoadjuvant) chemoradiation therapy is recommended for stage IIB and III tumors in fit patients. The preferred neoadjuvant chemotherapy regimen used with radiation is weekly carboplatin plus paclitaxel (Table 39–2). As an alternative, a combination of cisplatin plus 5-fluorouracil may be used along with radiation. When radiation therapy is considered, techniques that are less toxic such as intensity-modulated radiation therapy (IMRT) or proton beam therapy may be considered. Perioperative chemotherapy without radiation may also be considered for tumors of the gastroesophageal junction based on the randomized, multicenter, phase III MAGIC trial.

2. Chemotherapy plus radiation therapy without surgery—Combined treatment with chemotherapy and radiation achieves long-term survival rates in up to 25% of patients and is superior to radiation alone. Chemoradiation alone should be considered in patients with localized disease (stage II or IIIA) who are poor surgical candidates due to serious medical illness or poor functional status (Eastern Cooperative Oncology Group score greater than 2). Patients with cervical esophageal cancers, which appear similar biologically to head and neck cancers and in whom surgery is highly morbid and typically not recommended, also should be considered for chemoradiation.

3. Supportive care during definitive therapy—Patients with significant tumor obstruction may require percutaneous gastric or jejunal tube placement to maintain adequate hydration and nutrition during neoadjuvant chemoradiation or chemotherapy. Multidisciplinary consultation is required to determine the optimal procedure and to optimize perioperative nutrition.

B. Therapy for Incurable Disease

More than half of patients have either locally extensive tumor spread (T4b) that is unresectable or distant metastases (M1) at the time of diagnosis. Surgery is not warranted in these patients. Since prolonged survival can be achieved in few patients, the primary goal is to provide relief from dysphagia and pain, optimize quality of life, and minimize treatment side effects. The optimal palliative approach depends on the presence or absence of metastatic disease, expected survival, patient preference, and institutional experience.

1. Chemotherapy or chemoradiation—Combined radiation therapy and chemotherapy may achieve palliation in two-thirds of patients but is associated with significant side effects. It should be considered for patients with locally

advanced tumors without distant metastases who have good functional status and no significant medical problems, in whom prolonged survival may be achieved. Combination chemotherapy may be considered in patients with metastatic disease who still have good functional status and expected survival of at least several months.

The systemic therapy treatment options are the same for metastatic esophageal, gastroesophageal junction, and gastric cancers (Table 39–2). Choice of treatment is increasingly influenced by the results of molecular testing, including PD-L1 expression, mismatch repair/microsatellite instability (MSI) and, for adenocarcinomas, HER2 amplification testing. Because of the number of targetable alterations, a next generation sequencing panel should be considered. In patients with amplification of the *HER2* gene (approximately 15% of cases), addition of the monoclonal antibody trastuzumab (see Chapter 17) to chemotherapy is associated with prolonged survival. For patients without *HER2* amplification who have increased PD-L1 expression, the addition of a PD-1 or PD-L1 targeted antibody to chemotherapy may improve overall survival. Immunotherapy with pembrolizumab should be considered for tumors with either microsatellite instability-high (MSI-H) or deficient mismatch repair protein expression (dMMR). For patients with poor functional status, single-agent therapy with a fluoropyrimidine, a taxane, or irinotecan may be used.

2. Local therapy for esophageal obstruction—Patients with advanced esophageal cancer often have a poor functional and nutritional status. Radiation therapy alone to the area of esophageal obstruction may afford short-term relief of pain and dysphagia. Rapid palliation of dysphagia may be achieved by peroral placement of permanent expandable wire stents (alone or followed by radiation). However, placement of these stents is complicated by perforation, migration, or tumor ingrowth in up to 40% of cases.

► Prognosis

The overall 5-year survival rate of esophageal carcinoma is less than 20%. Apart from distant metastasis (M1b), the two most important predictors of poor survival are adjacent mediastinal spread (T4) and lymph node involvement. Whereas cure may be achieved in patients with regional lymph node involvement (stages IIB and III), involvement of nodes outside the chest (M1a) is indicative of metastatic disease (stage IV) that is incurable. For those patients whose disease progresses despite chemotherapy, meticulous efforts at palliative care are essential (see Chapter 5).

► When to Refer

- Patients should be referred to a gastroenterologist for evaluation and staging (endoscopy with biopsy, EUS) and palliative endoscopic stenting.
- Patients with curable and resectable disease for whom neoadjuvant therapy may be appropriate (stage IIB or IIIA) should be referred to medical, radiation, and surgical oncologists for consideration of neoadjuvant chemotherapy, chemoradiotherapy, and surgical resection.

- Patients with metastatic disease should be referred to medical and radiation oncologists for consideration of palliative chemotherapy or chemoradiation.
- Patients with metastatic disease and obstructive tumors not amenable to or refractory to palliative radiation or stenting may require referral to an interventional radiologist, gastroenterologist, or surgeon for gastric or jejunal tube placement for liquid artificial nutrition. Early referral to palliative care services may improve symptom management in patients with advanced or metastatic disease.

► When to Admit

Patients with high-grade esophageal obstruction with inability to manage oral secretions or maintain hydration should be admitted. Acute complications such as perforation, bleeding, aspiration, or fistula also may require admission.

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Gottlieb-Vedi E et al. Long-term survival in esophageal cancer after minimally invasive compared to open esophagectomy: a systematic review and meta-analysis. Ann Surg. 2019;270:1005. [PMID: 30817355]

Mariette C et al; Fédération de Recherche en Chirurgie (FRENCH) and French Eso-Gastric Tumors (FREGAT) Working Group. Hybrid minimally invasive esophagectomy for esophageal cancer. N Engl J Med. 2019;380:152. [PMID: 30625052]

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National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Esophageal and esophagogastric junction cancers. Version 5.2020. 2020 December 23. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf

GASTRIC ADENOCARCINOMA

ESSENTIALS OF DIAGNOSIS

- Dyspeptic symptoms with weight loss in patients over age 40 years.
- Iron deficiency anemia: occult blood in stools.
- Abnormality detected on upper gastrointestinal series or endoscopy.

► General Considerations

Gastric adenocarcinoma is the third most common cause of cancer death worldwide. However, its incidence has declined rapidly over the last 70 years, especially in Western countries, which may be attributable to changes in diet (more fruits and vegetables), food refrigeration (allowing

more fresh foods and reduced salted, smoked, and preserved foods), reduced toxic environmental exposures, and a decline in *Helicobacter pylori* infections. The incidence of gastric cancer remains high (62/100,000 males) in Japan and many developing regions, including eastern Asia, Eastern Europe, Chile, Colombia, and Central America. In the United States, there were an estimated 27,600 new cases and 11,010 deaths in 2020. The incidence is higher in Asian Americans, Hispanics, African Americans, and Native Americans (including Native Alaskans).

There are two main histologic variants of gastric cancer: “intestinal-type” (which resembles intestinal cancers in forming glandular structures) and “diffuse” (which is poorly differentiated, has signet-ring cells, and lacks glandular formation). The incidence of **intestinal-type gastric cancer** has declined significantly, but it is still the more common type (70–80%); it occurs twice as often in men as women, primarily affects older people (mean age 68 years), and is more strongly associated with environmental factors. It is believed to arise through a gradual, multi-step progression from inflammation (most commonly due to *H pylori*), to atrophic gastritis, to intestinal metaplasia, and finally to dysplasia and cancer. Chronic *H pylori* gastritis is the strongest risk factor for gastric carcinoma, increasing the relative risk 3.5- to 20-fold. It is estimated that 60–90% of cases of gastric carcinomas may be attributable to *H pylori*. Other risk factors for intestinal-type gastric cancer include pernicious anemia, a history of partial gastric resection more than 15 years previously, smoking, and diets that are high in nitrates or salt and low in vitamin C. **Diffuse gastric cancer** accounts for 20–30% of gastric cancer cases. In contrast to intestinal-type cancer, it affects men and women equally, occurs more commonly in young people, is not as strongly related to *H pylori* infection, and has a worse prognosis than intestinal-type cancer due to early metastasis. Most diffuse gastric cancers are attributable to acquired or hereditary mutations in the genes regulating the E-cadherin cell adhesion protein. Hereditary diffuse gastric cancer accounts for 1–3% of gastric cancers. The cancer may arise at a young age, is often multifocal and infiltrating with signet ring cell histology, and confers poor prognosis. Many of these families have a germline mutation of E-cadherin *CDH1*, which is inherited in an autosomal dominant pattern and carries a greater than 60% lifetime risk of gastric cancer. Prophylactic gastrectomy should be considered in patients known to carry this mutation.

Most gastric cancers arise in the body and antrum. These may occur in a variety of morphologic types: (1) polypoid or fungating intraluminal masses; (2) ulcerating masses; (3) diffusely spreading (**linitis plastica**), in which the tumor spreads through the submucosa, resulting in a rigid, atonic stomach with thickened folds (prognosis dismal); and (4) superficially spreading or “early” gastric cancer—confined to the mucosa or submucosa (with or without lymph node metastases) and associated with a favorable prognosis. *HER2* amplification and overexpression is seen in 10–25% of gastric adenocarcinoma cases and is more commonly observed in intestinal histology and moderately differentiated disease. Testing for MSI,

deficiency in mismatch repair proteins (dMMR), and PD-L1 is recommended in advanced disease to identify tumors that may respond to immunotherapy. For gastric adenocarcinoma, MSI-H/dMMR is found in 8–16% of cases.

In contrast to the dramatic decline in cancers of the distal stomach, a rise in incidence of tumors of the gastric cardia has been noted. These tumors have demographic and pathologic features that resemble Barrett-associated esophageal adenocarcinomas (see Esophageal Cancer).

► Clinical Findings

A. Symptoms and Signs

Gastric carcinoma is generally asymptomatic until the disease is quite advanced. Symptoms are nonspecific and are determined in part by the location of the tumor. Dyspepsia, vague epigastric pain, anorexia, early satiety, and weight loss are the presenting symptoms in most patients. Patients may derive initial symptomatic relief from over-the-counter remedies, further delaying diagnosis. Ulcerating lesions can lead to acute gastrointestinal bleeding with hematemesis or melena. Pyloric obstruction results in postprandial vomiting. Lower esophageal obstruction causes progressive dysphagia. Physical examination is rarely helpful. Stools may be guaiac positive.

B. Laboratory Findings

Iron deficiency anemia due to chronic blood loss or anemia of chronic disease is common. Circulating tumor markers do not have established clinical validity in screening or diagnosis of gastric cancer. However, when checked serially, tumor markers can assist in monitoring treatment response.

C. Endoscopy

Upper endoscopy should be obtained in all patients over age 60 years with new onset of epigastric symptoms (dyspepsia) and young patients with “alarm” symptoms (dysphagia, recurrent vomiting, significant weight loss), especially in immigrants from countries with a high prevalence of gastric cancer. Endoscopy with biopsies of suspicious lesions is highly sensitive for detecting gastric carcinoma. It can be difficult to obtain adequate biopsy specimens in diffuse type gastric cancer.

D. Imaging

Once a gastric cancer is diagnosed, preoperative evaluation with contrast CT of chest, abdomen, and pelvis and EUS is indicated to delineate the local extent of the primary tumor as well as to evaluate for nodal or distant metastases. EUS is superior to CT in determining the depth of tumor penetration and is useful for evaluation of early gastric cancers that may be removed by endoscopic mucosal resection. PET or combined PET-CT imaging is recommended for detection of distant metastasis.

► Screening

Because of its unproven efficacy and cost-effectiveness, screening for *H pylori* infection and treating it to prevent

gastric cancer is not recommended for asymptomatic adults in the general population but may be considered in patients who have immigrated from regions with a high incidence of gastric cancer or who have a family history of gastric cancer. Because of the high incidence of gastric carcinoma in Japan, screening upper endoscopy is performed there to detect early gastric carcinoma. Approximately 40% of tumors detected by screening are early, with a 5-year survival rate of almost 90%. Screening is not recommended in the United States.

► Staging

The TNM system is the commonly used classification to stage gastric adenocarcinoma. Staging is important not only because it correlates with the patient's long-term survival but also because it is used to determine which patients should receive adjuvant or neoadjuvant therapy.

A staging laparoscopy prior to definitive surgery to exclude peritoneal carcinomatosis should be considered in patients with stage T1b or greater disease without radiographic evidence of distant metastases. Pathologic review should include (1) grade of tumor, (2) histologic subtype, (3) depth of invasion, (4) whether lymphatic or vascular invasion is present, and (5) if there is known metastatic disease, the status of HER2 protein expression by immunohistochemistry or fluorescent in situ hybridization or both, along with MMR or MSI testing and PD-L1 protein expression.

► Differential Diagnosis

Ulcerating gastric adenocarcinomas are distinguished from benign gastric ulcers by biopsies. Approximately 3% of gastric ulcers initially believed to be benign later prove to be malignant. All gastric ulcers identified at endoscopy should be biopsied to exclude malignancy. Ulcers that are suspicious for malignancy to the endoscopist or that have atypia or dysplasia on histologic examination warrant repeat endoscopy in 2–3 months to verify healing and exclude malignancy. Nonhealing ulcers should be considered for resection. Infiltrative carcinoma with thickened gastric folds must be distinguished from lymphoma and other hypertrophic gastropathies.

► Treatment

A. Curative Surgical Resection

Surgical resection is the only therapy with curative potential. Laparoscopic techniques achieve similar outcomes and lower overall complication rates as open gastrectomy. In Japan and in specialized centers in the United States, endoscopic mucosal resection is performed in select patients with small (less than 1–2 cm), early (intramucosal or T1aN0) gastric cancers after careful staging with EUS. Approximately 25% of patients undergoing surgery will be found to have locally unresectable tumors or peritoneal, hepatic, or distant lymph node metastases that are incurable. The remaining patients with confirmed localized disease should undergo radical surgical resection. For adenocarcinoma localized to the distal two-thirds of the stomach, a subtotal gastrectomy should be performed. For

proximal gastric cancer or diffusely infiltrating disease, total gastrectomy is necessary. The ultimate goal of surgery is obtaining negative surgical margins. Vitamin B₁₂ supplementation is required after gastrectomy. For patients with localized gastric cancer that is resectable, current National Comprehensive Cancer Network (NCCN) treatment guidelines recommend gastrectomy with extended (D1), or modified regional (D2), lymph node dissection and sampling of 15 or more lymph nodes. D2 lymphadenectomy has been shown to improve disease-specific survival but is associated with increased postoperative mortality.

B. Perioperative Chemotherapy or Chemoradiation

The use of perioperative chemotherapy or adjuvant chemoradiation is associated with improved survival in patients with localized or locoregional gastric adenocarcinoma who undergo surgical resection. The choice of treatment depends on the location and extent of tumor, type of surgery, patient comorbidities and performance status, and institutional experience. Tumors arising in the gastroesophageal junction are treated following algorithms for esophageal primary tumors. Multidisciplinary treatment decision making involving the surgeon, radiation oncologist, and medical oncologist is imperative.

C. Palliative Modalities

Many patients will be found either preoperatively or at the time of surgical exploration to have advanced disease that is not amenable to curative intent surgery due to peritoneal or distant metastases or local invasion of other organs. In some of these cases, palliative resection of the tumor nonetheless may be indicated to alleviate pain, bleeding, or obstruction. For patients with unresectable disease, a surgical diversion with gastrojejunostomy may be indicated to prevent obstruction. Alternatively, unresected tumors may be treated with endoscopic stent therapy, radiation therapy, or angiographic embolization to relieve bleeding or obstruction. Systemic therapy may be considered in patients with metastatic disease who still have good functional status and expected survival of at least several months. The regimens used are the same as those for esophageal and gastroesophageal junction tumors discussed above (Table 39–2).

► Prognosis

The 5-year survival for gastric cancer varies greatly by stage, location, and histologic features. The 5-year survival is approximately 90% for early-stage cancer (T1b or less), 80% for stage II after curative intent treatment, but less than 20% for stage IIIC. Even with apparently localized disease, proximal tumors have a 5-year survival of less than 15%. For those whose disease progresses despite therapy, meticulous efforts at palliative care are essential (see Chapter 5).

► When to Refer

- Patients with dysphagia, weight loss, protracted vomiting, iron deficiency anemia, melena, or new-onset dyspepsia (especially if aged 60 years or older or associated

with other alarm symptoms) in whom gastric cancer is suspected should be referred for endoscopy.

- Patients should be referred to a surgeon for attempt at curative resection in stage I, II, or III cancer, including staging laparoscopy if indicated.
- Prior to surgery, patients should be referred to an oncologist to determine the role for perioperative chemoradiation or chemotherapy.
- Patients who have undergone gastrectomy require consultation with a nutritionist due to propensity for malnutrition and complications, such as dumping syndrome and vitamin B₁₂ deficiency, postoperatively.
- Patients with unresectable or metastatic disease should be referred to an oncologist for consideration of palliative chemotherapy or chemoradiation. Early referral to palliative care services may also be considered for symptom management in patients with advanced and metastatic disease.

► When to Admit

Patients with acute bleeding, protracted vomiting, or inability to maintain hydration or nutrition.

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Katai H et al. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open-distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer: a multicentre, non-inferiority, phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2020;5:142. [PMID: 31757656]

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National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Gastric Cancer. Version 4.2020. 2020 December 23. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

GASTRIC LYMPHOMA

ESSENTIALS OF DIAGNOSIS

- Symptoms of dyspepsia, weight loss, or anemia.
- Variable abnormalities on upper gastrointestinal series or endoscopy including thickened folds, ulcer, mass, or infiltrating lesions; diagnosis established by endoscopic biopsy.
- Abdominal CT and EUS required for staging.

► General Considerations

Gastric lymphomas may be primary (arising from the gastric mucosa) or may represent a site of secondary involvement in patients with nodal lymphomas. Distinguishing advanced primary gastric lymphoma with adjacent nodal spread from advanced nodal lymphoma with secondary

gastric spread is essential because the prognosis and treatment of primary and secondary gastric lymphomas are different. Primary gastric lymphoma is the second most common gastric malignancy, accounting for 3–5% of gastric cancers. More than 95% of these are non-Hodgkin B-cell lymphomas mainly consisting of either mucosa-associated lymphoid tissue (MALT)-type lymphoma and diffuse large B-cell lymphoma. Over 90% of low-grade primary gastric MALT-type lymphomas are associated with *H pylori* infection. Gastric T-cell lymphoma, which is associated with HTLV-1 infection, is rare and makes up 7% of primary gastric lymphomas.

Clinical Findings & Staging

The clinical presentation and endoscopic appearance of gastric lymphoma are similar to those of adenocarcinoma. Most patients have abdominal pain, weight loss, or bleeding. Patients with diffuse large B-cell lymphoma are more likely to have systemic symptoms and advanced tumor stage. At endoscopy, lymphoma may appear as an ulcer, mass, or diffusely infiltrating lesion. It tends to have horizontal infiltration as opposed to the vertical extension seen in adenocarcinoma. The diagnosis is established with endoscopic biopsy; FNA is not adequate. Since the disease can be multifocal, biopsies of both suspicious and normal-appearing areas are recommended. Biopsy specimens should be tested for *H pylori* and, if positive, for t(11;18) via PCR or FISH. EUS is the most sensitive test for determining the level of invasion and presence of perigastric lymphadenopathy and should be performed for accurate staging, if available. All patients should undergo staging with CT scanning of chest, abdomen, and pelvis. For gastric MALT lymphomas, the Lugano staging system is most frequently used. Stage I is confined to the gastrointestinal tract, stage II involves local or regional lymph nodes, stage IIE has invasion of adjacent organs or tissues, and stage IV has distant metastases. There is no stage III. For patients with diffuse large B-cell lymphomas involving the stomach, combination PET-CT imaging, bone marrow biopsy with aspirate, tumor lysis laboratory tests, and hepatitis B and HIV serologies also may be required for staging and treatment planning (see Chapter 13).

Treatment

Treatment of primary gastric lymphomas depends on the tumor histology, grade, and stage. Marginal B-cell lymphomas of the MALT type that are low-grade and localized to the stomach wall (stage I) or perigastric lymph nodes (stage IIE₁) have an excellent prognosis. Patients with primary gastric MALT-lymphoma should be tested for *H pylori* infection and treated if positive. Complete lymphoma regression after successful *H pylori* eradication occurs in approximately 75% of cases of stage I and approximately 55% with stage IIE low-grade lymphoma. However, 95% of cancers positive for t(11;18) do not respond to antibiotics. Remission may take as long as a year, and relapse occurs in about 2% of cases per year. Many patients with minimal disease after successful *H pylori* eradication may be observed closely without further therapy. Restaging

with endoscopy and biopsy is recommended 3 months after antibiotic treatment and 3–6 months following radiation therapy. Ultimately, endoscopic surveillance after treatment is recommended every 3–6 months for 5 years to evaluate for recurrence.

In patients whose tumors harbor specific gene translocations, including t(11;18) (API2-MALT1), t(1;14), or t(14;18), rates of remission after *H pylori* eradication are lower, and treatment with radiation is often required.

The long-term survival of low-grade MALT lymphoma for stage I is over 90% and for stage II is 35–65%. Surgical resection is not recommended. Diffuse large B-cell or other higher-grade lymphomas with secondary gastrointestinal involvement usually present at an advanced stage with widely disseminated disease and are treated according to stage and subtype of lymphoma (see Chapter 13).

Avilés A et al. Primary gastric diffuse large B-cell lymphoma: the role of dose-dense chemotherapy. *J Oncol Pharm Pract.* 2019; 25:1682. [PMID: 30370804]

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GASTRIC NEUROENDOCRINE TUMORS

Gastric NETs make up less than 1% of gastric neoplasms. They may occur sporadically or secondary to chronic hypergastrinemia that results in hyperplasia and transformation of enterochromaffin cells in the gastric fundus. The majority of NETs are caused by hypergastrinemia and occur in association with either pernicious anemia (75%) (type 1) or Zollinger-Ellison syndrome (5%) (type 2). Type 1 tumors are associated with chronic atrophic gastritis, gastric achlorhydria, and secondary hypergastrinemia. Initial diagnostic workup includes serum gastrin level, upper endoscopy, and EUS. Gastrin level should be obtained 1 week after the patient has stopped taking protein pump inhibitors. For low-grade tumors (Ki-67 less than 3% or less than 2 mitoses/10 high-power fields [HPF]), somatostatin receptor-based imaging (somatostatin receptor scintigraphy or gallium-68 dotate PET/CT) should be performed. For high-grade tumors (Ki-67 greater than 20% or greater than 20 mitoses/10 HPF), FDG-PET/CT is preferred to evaluate the extent of disease.

For patients with hypergastrinemia (suspected of type 1 or type 2 carcinoid), serum vitamin B₁₂ and intrinsic factor antibody levels should be obtained to exclude pernicious anemia. Gastric NETs associated with Zollinger-Ellison

syndrome occur almost exclusively in patients with multiple endocrine neoplasia type 1 (MEN 1), in which chromosomal loss of 11q13 has been reported. Gastric NETs caused by hypergastrinemia tend to be multifocal, be smaller than 1 cm, have a low potential for metastatic spread, and thus are unlikely to cause development of the carcinoid syndrome. Small lesions may be successfully treated with endoscopic resection followed by endoscopic surveillance every 6–12 months, or with observation. Antrectomy reduces serum gastrin levels and may lead to regression of small tumors. It can be considered in patients with type 1 gastric NETs to reduce recurrence risk and frequency of post-therapy monitoring. Octreotide therapy may be appropriate for patients with underlying gastrinoma and Zollinger-Ellison syndrome. Patients with tumors larger than 2 cm should undergo endoscopic or surgical resection (see Small Intestinal Adenocarcinomas below).

Type 3 gastric NETs arise sporadically, independent of gastrin production, and account for up to 20% of gastric NETs. Most sporadic gastric NETs are solitary, larger than 2 cm, and have a strong propensity for hepatic or pulmonary metastases and thus the carcinoid syndrome at initial presentation. CT or MRI should be obtained to evaluate for metastatic disease. Localized sporadic NETs should be treated with partial or total gastrectomy and regional lymphadenectomy. Advanced, low-grade gastric NETs can be monitored with serial scans, if asymptomatic. Somatostatin analogs may provide symptomatic relief for patients with functional gastric NETs. Advanced high-grade gastric neuroendocrine carcinomas are treated in a fashion similar to SCLCs.

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GASTROINTESTINAL MESENCHYMAL TUMORS

Pathobiology & Diagnosis

Gastrointestinal mesenchymal tumors (which include stromal tumors, leiomyomas, and schwannomas) derive from mesenchymal stem cells and have an epithelioid or spindle cell histologic pattern, resembling smooth muscle. The most common stromal tumors are gastrointestinal stromal tumors (“GISTs”), which originate from interstitial cells of Cajal. GISTs occur throughout the gastrointestinal tract, but most commonly in the stomach (60%) and small intestine (30%). Approximately 80% of GISTs have mutations in *KIT*. A percentage of the *KIT* wild type tumors have a mutation in *PDGFRA*, and only a minority of patients are wild type for both genes. Mesenchymal tumors may be discovered incidentally on imaging studies or endoscopy or may cause symptoms (most commonly bleeding, pain, or obstruction). At endoscopy, they appear as a submucosal

mass that may have central umbilication or ulceration. EUS with guided FNA biopsy is the optimal study for diagnosing gastric mesenchymal tumors and distinguishing them from other submucosal lesions. Percutaneous biopsy may confer risk of bleeding or intra-abdominal seeding. CT of the abdomen and pelvis with contrast, MRI, and PET imaging are useful in the diagnosis and staging. PET imaging also may be useful to monitor response to treatment.

While almost all GISTs have malignant potential, the risk of developing metastasis is increased with tumor size greater than 2 cm, nongastric location, and mitotic index greater than 5 mitoses per 50 HPF. It is difficult to distinguish benign from malignant tumors by EUS appearance or by FNA. But, in general, lesions are more likely benign if they are smaller than 2 cm, have a smooth border, and have a homogeneous echo pattern on EUS. Resection settles the issue.

Treatment

A. Localized Treatment

Surgery is recommended for all patients with tumors that are 2 cm or larger, increasing in size, have an EUS appearance suspicious for malignancy, or are symptomatic. The management of asymptomatic gastric lesions 2 cm or smaller in size depends on the EUS features. Tumors with high-risk EUS features can be surgically resected. If no high-risk features are noted, endoscopic surveillance can be performed. Because of the low but real long-term risk of malignancy, surgical resection should be considered in younger, otherwise healthy patients. However, other patients may be monitored with serial endoscopic ultrasonographic examinations or, in select cases, endoscopic resections. After complete surgical resection, the risk of GIST recurrence can be calculated based on tumor location, size, and mitotic index. The majority of recurrences occur within the first 3 years.

B. Systemic Treatment

Because the majority of GISTs are driven by mutations in *KIT* or *PDGFRA*, the tyrosine kinase inhibitor, imatinib, which blocks signaling through this pathway, is used across disease stages. Neoadjuvant therapy with imatinib may be considered for patients with localized GIST tumors who are deemed to be at high risk for resection because of comorbidities, tumor size, or tumor location. A biopsy is required to confirm the diagnosis of GIST prior to initiation of neoadjuvant imatinib. Adjuvant therapy with imatinib delays recurrence and prolongs survival, but it is not likely to be curative.

Untreated metastatic GIST tumors are aggressive and carry a poor prognosis. However, imatinib induces disease control in up to 85% of patients with metastatic disease with a progression-free survival of 20–24 months and median overall survival of almost 5 years. Additionally, imatinib is associated with long-term survival in some patients. One study reported that 18% of patients continued treatment after a median follow-up of 9 years. For patients with imatinib-resistant cancers, high-dose imatinib or other approved tyrosine kinase inhibitors (eg, sunitinib or regorafenib) are options.

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MALIGNANCIES OF THE SMALL INTESTINE

The frequency of different tumor types varies by location within the small intestine. Adenocarcinomas are most common in the duodenum and jejunum and neuroendocrine tumors, in the ileum. Lymphomas and sarcomas each have similar incidences in the various segments of the small intestine.

1. Small Intestinal Adenocarcinomas

These tumors often present with nonspecific symptoms such as abdominal pain and nausea. The incidence is rare, with 11,110 new diagnoses estimated in 2020 in the United States. These adenocarcinomas are most often diagnosed at stage III or IV, but their prognosis is slightly worse than for similar stage colon adenocarcinoma. The duodenum is the most common site of small bowel adenocarcinoma, specifically in the periamppullary region. Ampullary carcinoma may present with jaundice due to bile duct obstruction or bleeding. Surgical resection of early lesions is curative in up to 40% of patients.

The management of nonampullary small intestinal adenocarcinoma is extrapolated from data available for the management of colon adenocarcinoma.

2. Small Intestinal Lymphomas

Lymphomas may arise primarily in the gastrointestinal tract or may involve it secondarily in patients with disseminated disease. In Western countries, primary gastrointestinal lymphomas account for 5% of lymphomas and 20% of small bowel malignancies. There is an increased incidence of small intestinal lymphomas in patients with AIDS, Crohn disease, and those receiving immunosuppressive therapy. The most common histologic subtype is non-Hodgkin extranodal marginal zone (MALT) B-cell lymphoma. That said, enteropathy-associated T-cell lymphomas appear to be increasing in incidence in the United States. They are associated with the diagnosis of celiac disease. In the Middle East, lymphomas may arise in the setting of immunoproliferative small intestinal disease. Other types of intestinal lymphomas include primary intestinal follicular cell lymphoma, mantle cell lymphoma, and Burkitt lymphoma (see Chapter 13).

Presenting symptoms or signs of primary small bowel lymphoma include abdominal pain, weight loss, nausea and vomiting, distention, anemia, and occult blood in the

stool. Fevers are unusual. Protein-losing enteropathy may result in hypoalbuminemia, but other signs of malabsorption are unusual. Barium radiography or CT enterography helps localize the site of the lesion. The diagnosis requires endoscopic, percutaneous, or laparoscopic biopsy. Imaging and possibly bone marrow biopsy are required to determine stage.

Treatment depends on the tumor histologic subtype and stage of disease (see Chapter 13). If feasible, surgical resection of primary intestinal lymphoma, may be appropriate for localized tumors. In patients with limited disease (stage IE) in whom resection is performed with negative margins, the role of adjuvant chemotherapy is unclear. Locoregional radiation should be considered if surgical margins are positive. Patients with more extensive disease generally are treated according to the tumor histology.

3. Intestinal Neuroendocrine Tumors



ESSENTIALS OF DIAGNOSIS

- ▶ Majority are asymptomatic and discovered incidentally at endoscopy or surgery.
- ▶ Carcinoid syndrome occurs in < 10%; hepatic metastases are generally present.
- ▶ Risk of metastasis is related to tumor size and location.

General Considerations

Neuroendocrine tumors are the most common type of tumor arising in the small bowel. Gastrointestinal NETs (also called carcinoids) most commonly occur in the small intestine (45%) but are also found in the rectum (20%), appendix (17%), and colon (11%), with the remainder occurring in the stomach (less than 10%; see Gastric Neuroendocrine Tumors above). Carcinoid tumors are well-differentiated neuroendocrine tumors that may secrete a variety of hormones, including serotonin, somatostatin, gastrin, and substance P.

Small intestinal carcinoids most commonly arise in the distal ileum within 60 cm of the ileocecal valve. Up to 30% are multicentric. The risk of metastatic spread increases when the tumor is 1 cm or larger and when it is larger than 2 cm with invasion beyond the muscularis propria. Appendiceal carcinoids are identified in 0.3% of appendectomies, usually as an incidental finding. Almost 80% of these tumors are smaller than 1 cm, and 90% are smaller than 2 cm. However, in patients with appendiceal carcinoid tumors larger than 2 cm, approximately 90% develop nodal and distant metastases; right hemicolectomy is recommended in these cases.

Rectal carcinoids are usually detected incidentally as submucosal nodules during proctoscopic examination and often locally excised by biopsy or snare polypectomy before the histologic diagnosis is known. Rectal carcinoids smaller than 1 cm virtually never metastasize and are treated effectively with local endoscopic or transanal excision. Larger tumors are associated with the development of metastasis

in 10%. Hence, a more extensive cancer resection operation is warranted in fit patients with rectal carcinoid tumors larger than 1–2 cm or with high-risk features (such as invasion of muscularis propria or evidence of nodal involvement), or both.

► Clinical Findings

A. Symptoms and Signs

Most lesions smaller than 1–2 cm are asymptomatic and difficult to detect by endoscopy or imaging studies. Small intestinal carcinoids may present with intermittent abdominal pain, bowel obstruction, bleeding, or bowel infarction. Appendiceal and rectal carcinoids usually are small and asymptomatic, but large lesions can cause bleeding, obstruction, or altered bowel habits. **Carcinoid syndrome** occurs in less than 10% of patients. More than 90% of patients with carcinoid syndrome have hepatic metastases, usually from carcinoids of small bowel origin. About 10% of patients with carcinoid syndrome have primary bronchial or ovarian tumors without hepatic metastases. Carcinoid syndrome is caused by tumor secretion of hormonal mediators. The manifestations include facial flushing, edema of the head and neck (especially with bronchial carcinoid), abdominal cramps and diarrhea, bronchospasm, cardiac lesions (pulmonary or tricuspid stenosis or regurgitation in 10–30%), and telangiectases.

B. Laboratory Findings

Serum chromogranin A is elevated in the majority of NETs, although its sensitivity for small, localized carcinoid tumors is unknown. Serum chromogranin A is elevated in almost 90% of patients with advanced small bowel carcinoid. Urinary 5-hydroxyindoleacetic acid (5-HIAA) and platelet serotonin levels are also elevated in patients with metastatic carcinoid; however, these tests are less sensitive than serum chromogranin A. There is increased urinary 5-HIAA in carcinoid syndrome; symptomatic patients usually excrete more than 25 mg of 5-HIAA per day in the urine. Because certain foods and medications can interfere with 5-HIAA levels, these should be withheld for 48 hours prior to a 24-hour urine collection.

C. Imaging

Abdominal CT may demonstrate a mesenteric mass with tethering of the bowel, lymphadenopathy, and hepatic metastasis. Abdominal CT or enterography may reveal kinking of the bowel, but because the lesion is extraluminal, the diagnosis may be overlooked for several years. Gallium Ga-68 DOTATATE PET scan has replaced somatostatin receptor scintigraphy as the standard of care for staging; however, both may help identify disease that may benefit from treatment with somatostatin analogs or peptide receptor radionuclide therapy (PRRT).

► Treatment & Outcomes

Small intestinal carcinoids generally are indolent tumors with slow spread. Patients with disease confined to the small intestine should be treated with surgical excision.

There is no proven role for adjuvant therapy after complete resection. Five-year survival rates for patients with stage I and II disease are 96% and 87%, respectively. In patients with resectable disease who have lymph node involvement (stage III), the 5-year survival rate is 74%; however, by 25 years, less than 25% remain disease free. Across stages, prognosis is strongly associated with histologic differentiation and grade. Patients with grade 1 disease may not require treatment for many years even with metastatic disease. However, patients with a grade 3 neuroendocrine tumor may have a clinical course more similar to a high-grade neuroendocrine carcinoma.

In patients with advanced disease, therapy historically has been deferred until the patient is symptomatic. Conventional cytotoxic chemotherapy agents do not achieve significant responses in carcinoid tumors and have not been associated with improved outcomes. For patients who are symptomatic either from tumor bulk or carcinoid syndrome, the cornerstone of therapy is typically a long-acting somatostatin analog, which inhibits hormone secretion from the carcinoid tumor. In 90% of patients, this results in dramatic relief of symptoms of carcinoid syndrome, including diarrhea or flushing, and may also control tumor growth for a median period of 1 year. Options at disease progression include octreotide dose escalation, or addition of everolimus, a mammalian target of rapamycin (mTOR) inhibitor. For patients with somatostatin receptor-positive disease based on imaging, another option after progression is treatment with PRRT. PRRT consists of a somatostatin analog conjugated to a radioactive isotope such as yttrium-90 or lutetium-177. Studies of anti-angiogenic kinase inhibitors have shown some benefit; currently, sunitinib is approved in the United States for pancreatic neuroendocrine tumors.

In selected patients with hepatic-dominant disease, resection of hepatic metastases may provide dramatic improvement in carcinoid syndrome symptoms. Tumor debulking with liver-directed chemoembolization or radioembolization may also provide symptomatic improvement in some of these patients.

Patients with advanced, poorly differentiated intestinal NETs are treated in a similar fashion to those with small cell carcinomas. They have a poor prognosis.

4. Small Intestine Sarcoma

Sarcomas constitute approximately 10% of small bowel neoplasms and are commonly found in the jejunum and ileum (and in a Meckel diverticulum, if present). Most arise from stromal tumors (GISTs) that stain positive for CD117; a minority arise from smooth muscle tumors (leiomyosarcomas) (see Gastrointestinal Mesenchymal Tumors above). Common symptoms of small intestine sarcoma include pain, weight loss, bleeding, and perforation. As the lesions tend to enlarge extraluminally, obstruction is rare.

Kaposi sarcoma was at one time a common complication in AIDS, but the incidence is declining with antiretroviral therapy. It can also occur in the setting of immunosuppression after organ transplantation. It is caused by infection with human herpesvirus 8 (HHV8). Lesions may be present anywhere in the intestinal tract.

Visceral involvement usually is associated with cutaneous disease. Most lesions are clinically silent; however, large lesions may be symptomatic. Widespread involvement may be best treated by systemic chemotherapy using single-agent therapy or combinations of pegylated-doxorubicin, paclitaxel, vincristine, bleomycin, or etoposide. Surgery or radiation may be indicated for isolated high-risk lesions.

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risk of cancer. Approximately 85% of sporadic colorectal cancers arise from adenomatous polyps. They have loss of function of one or more tumor suppressor genes (eg, *p53*, *APC*, or *DCC*) due to a combination of spontaneous mutation of one allele combined with chromosomal instability and aneuploidy (abnormal DNA content) that leads to deletion and loss of heterozygosity of the other allele (eg, 5q, 17q, or 18p deletion). Activation of oncogenes such as *KRAS* and *BRAF* is present in a subset of colorectal cancers with prognostic and therapeutic implications discussed further below.

Approximately 10–20% of colorectal cancers arise from serrated polyps, most of which have hypermethylation of CpG-rich promoter regions that leads to inactivation of the DNA mismatch repair gene *MLH1*, resulting in MSI, and activation of mutations of the *BRAF* gene. Serrated colon cancers have distinct clinical and pathologic characteristics, including diploid DNA content, predominance in the proximal colon, poor differentiation, and more favorable prognosis.

Up to 5% of colorectal cancers are caused by inherited germline mutations resulting in polyposis syndromes (eg, familial adenomatous polyposis) or hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome). These conditions are discussed further in Chapter 15.

Risk Factors

A number of factors increase the risk of developing colorectal cancer. Some of these factors include smoking, consumption of red and processed meats, alcohol intake, diabetes mellitus, physical inactivity, obesity, and history of inflammatory bowel disease. Recognition of these factors has had an impact on screening strategies. However, 75% of all cases occur in people with no known predisposing factors.

A. Age

The incidence of colorectal cancer rises sharply after age 45 years, and 90% of cases occur in persons over the age of 50 years. The median age at diagnosis is 68 for men and 72 for women. Over the past two decades there has been a 20% decrease in incidence among adults over age 50 (likely due to colorectal cancer screening programs) but a 50% increase in incidence among adults under age 50 (especially in the distal colon and rectum). The incidence of young adult-onset colorectal cancer is rising in all racial and ethnic groups but is highest in Blacks. In the United States, the colorectal cancer incidence rates in adults over age 50 is 40/100,000 and is 12.2/100,000 in adults younger than age 50. It is estimated that by 2030, 10% of colon cancer and 20% of rectal cancers will occur in patients under the age of 50. The reason for the increase in colorectal cancer incidence among adults under age 50 is uncertain.

B. Family History of Neoplasia

A family history of colorectal cancer is present in approximately 20% of patients with colon cancer. Hereditary factors are believed to contribute to 20–30% of colorectal cancers; however, the genes responsible for most of these cases have not yet been identified. Hereditary cancer

COLORECTAL CANCER

ESSENTIALS OF DIAGNOSIS

- ▶ Personal or family history of adenomatous or serrated polyps or colorectal cancer are important risk factors.
- ▶ Symptoms or signs depend on tumor location.
- ▶ **Proximal colon:** fecal occult blood, anemia.
- ▶ **Distal colon:** change in bowel habits, hematochezia.
- ▶ Diagnosis established with colonoscopy.

General Considerations

Colorectal cancer is the second leading cause of death due to malignancy in the United States. Colorectal cancer will develop in approximately 4.2% of Americans and has a 5-year survival rate of 65%. In 2020, there were an estimated 147,950 new cases of colorectal cancer in the United States, with an estimated 53,200 deaths. Between 1996 and 2010, its mortality rate decreased by 46%. A 2015 National Health Interview Survey estimated that 62% of US adults have undergone recommended screening. On average, new cases have been falling 3.2% each year over the last 10 years.

Colorectal cancers are almost all adenocarcinomas, which tend to form bulky exophytic masses or annular constricting lesions. The majority of colorectal cancers are thought to arise from malignant transformation of an adenomatous polyp (tubular, tubulovillous, or villous adenoma) or serrated polyp (hyperplastic polyp, traditional serrated adenoma, or sessile serrated adenoma). Polyps that are “advanced” (ie, polyps at least 1 cm in size, adenomas with villous features or high-grade dysplasia, or serrated polyps with dysplasia) are associated with a greater

syndromes (Lynch syndrome or polyposis syndromes) account for approximately 3–4% of colorectal cancers in patients 50 years or older but 10–15% of patients with young adult-onset colorectal cancer (see Chapter 15). Approximately 6% of the Ashkenazi Jewish population has a missense mutation in the *APC* gene (*APC I1307K*) that confers a modestly increased lifetime risk of developing colorectal cancer (odds ratio [OR] 1.4–1.9) that phenotypically resembles sporadic colorectal cancer rather than familial adenomatous polyposis. Genetic screening is available, and patients harboring the mutation merit more intensive colorectal screening.

A family history of colorectal cancer or adenomatous polyps is one of the most important risk factors for colorectal cancer. The risk of colon cancer is proportionate to the number and age of affected first-degree family members with colon neoplasia. People with one first-degree family member with colorectal cancer have an increased risk approximately two times that of the general population; however, the risk is almost four times if the family member was younger than 45 years when the cancer was diagnosed. Patients with two first-degree relatives have a fourfold increased, or 25–30% lifetime, risk of developing colon cancer. First-degree relatives of patients with adenomatous polyps also have a twofold increased risk for colorectal neoplasia, especially if they were younger than 60 years when the polyp was detected or if the polyp was 10 mm or larger.

C. Inflammatory Bowel Disease

The risk of adenocarcinoma of the colon begins to rise 8 years after disease onset in patients with ulcerative colitis and Crohn colitis (see Chapter 15). For this reason, initiation of surveillance with colonoscopy is recommended at 8–10 years after onset of inflammatory bowel disease symptoms.

D. Dietary and Lifestyle Factors and Chemoprevention

In epidemiologic studies, diets rich in fats and red meat are associated with an increased risk of colorectal adenomas and cancer, whereas diets high in fruits, vegetables, and fiber are associated with a decreased risk. However, prospective studies have not shown a reduction in colon cancer or recurrence of adenomatous polyps with diets that are low in fat; that are high in fiber, fruits or vegetables; or that include calcium, folate, beta-carotene, or vitamin A, C, D, or E supplements.

Meta-analyses suggest that individuals with increased physical activity are up to 27% less likely to develop colon cancer. There also is a correlation between increasing body mass index and cancer risk, such that for each increase of 5 kg/m² in BMI, there is a 5% increased cancer risk. Patients with higher levels of pre- and post-diagnosis physical activity experience reduced colorectal cancer-specific mortality and all-cause mortality. Maintaining a healthy body weight, a healthy diet, and a physically active lifestyle are recommended in colorectal cancer survivors.

Low-dose aspirin has been associated with a reduced risk of colorectal adenomas and cancer in multiple studies.

A 2016 USPSTF systematic review of controlled trials concluded that prolonged regular use of low-dose aspirin (81 mg/day) is associated with a 40% reduction in colorectal cancer incidence after 10 years and a 33% reduction in colorectal cancer mortality after 20 years. Because long-term aspirin use is associated with a low incidence of serious complications (gastrointestinal hemorrhage, stroke), low-dose aspirin should not be routinely administered as a chemopreventive agent without other medical indications. Low-dose aspirin may also be considered in patients with a personal or family history of colorectal cancer or advanced adenomas; however, its administration does not obviate the need for colonoscopy screening and surveillance.

E. Other Factors

The overall incidence of colorectal cancer is similar in men and women; however, similar incidence rates are reached in women about 4–6 years later than in men. A higher proportion of cancers are located in the proximal colon in women (46%) than men (37%). The incidence and mortality of colon adenocarcinoma is higher in Blacks and Native Americans than in Whites. It is unclear whether this is due to genetic or socioeconomic factors (eg, diet or reduced access to medical care).

► Clinical Findings

A. Symptoms and Signs

Adenocarcinomas grow slowly and may be present for several years before symptoms appear. However, some asymptomatic tumors may be detected by the presence of fecal occult blood (see Screening for Colorectal Neoplasms, below). Symptoms depend on the location of the carcinoma. Chronic blood loss from right-sided colonic cancers may cause iron deficiency anemia, manifested by fatigue and weakness. Obstruction, however, is uncommon because of the large diameter of the right colon and the liquid consistency of the fecal material. Lesions of the left colon often involve the bowel circumferentially. Because the left colon has a smaller diameter and the fecal matter is solid, obstructive symptoms may develop with colicky abdominal pain and a change in bowel habits. Constipation may alternate with periods of increased frequency and loose stools. The stool may be streaked with blood, though marked bleeding is unusual. With rectal cancers, patients note tenesmus, urgency, and recurrent hematochezia. Physical examination is usually normal except in advanced disease. The liver should be examined for hepatomegaly, suggesting metastatic spread. For cancers of the distal rectum, digital examination is necessary to determine whether there is extension into the anal sphincter or fixation, suggesting extension to the pelvic floor.

B. Laboratory Findings

A CBC should be obtained to look for anemia. Elevated liver biochemical tests raise suspicion of metastatic disease. The serum carcinoembryonic antigen (CEA) should be measured in all patients with proven colorectal cancer but is not appropriate for screening. The CEA is not elevated in

many patients with confirmed colorectal cancer; conversely, the CEA may be elevated in active smokers and those with a variety of other nonmalignant conditions. A preoperative CEA level greater than 5 ng/mL is a poor prognostic indicator. After complete surgical resection, CEA levels should normalize; persistently elevated levels suggest the presence of persistent disease and warrant further evaluation. CEA is routinely monitored at the time of adjuvant therapy and during postoperative surveillance for patients who had elevated levels before resection.

C. Colonoscopy

Colonoscopy is the required diagnostic procedure in patients with a clinical history suggestive of colorectal cancer or in patients with an abnormality suspicious for cancer detected on radiographic imaging. Colonoscopy and upper endoscopy should be considered in all adults with new-onset iron deficiency anemia. Colonoscopy permits biopsy for pathologic confirmation of malignancy.

D. Imaging

Chest, abdominal, and pelvic CT scans with contrast are required for preoperative staging. CT scans may demonstrate distant metastases but are less accurate in the determination of the level of local tumor extension (T stage) or lymphatic spread (N stage). Intraoperative assessment of the liver by direct palpation and ultrasonography can be performed to detect hepatic metastases (M stage). For rectal cancers (generally defined as tumors arising 12 cm or less proximal to the anal verge), pelvic MRI or endorectal ultrasonography is required to determine the depth of penetration of the cancer through the rectal wall (T stage) and perirectal lymph nodes (N stage), informing decisions about preoperative (neoadjuvant) chemoradiotherapy and operative management. PET is not routinely used for staging or surveillance in colorectal cancers.

► Staging

The TNM system is the commonly used classification to stage colorectal cancer. Staging is important not only because it correlates with the patient's long-term survival but also because it is used to determine which patients should receive adjuvant or neoadjuvant therapy.

► Differential Diagnosis

The nonspecific symptoms of colorectal cancer may be confused with those of irritable bowel syndrome, diverticular disease, ischemic colitis, inflammatory bowel disease, infectious colitis, and hemorrhoids. Neoplasm must be excluded in any patient over age 40 years who reports a change in bowel habits or hematochezia or who has an unexplained iron deficiency anemia or occult blood in stool samples.

► Treatment

A. Colon Cancer

Surgical resection of the colonic tumor is the treatment of choice for almost all patients. It may be curative in patients

with stage I, II, and III disease and even some patients with metastatic (stage IV) disease. Multiple studies demonstrate that minimally invasive, laparoscopically assisted colectomy results in similar outcomes and rates of recurrence to open colectomy. Regional dissection of at least 12 lymph nodes should be performed to determine staging, which guides decisions about adjuvant therapy. Following complete endoscopic removal of an adenomatous polyp (polypectomy) that is found on pathologic review to contain a focus of cancer (malignant polyp), observation is a reasonable alternative to further surgical resection in carefully selected patients with invasion into the submucosa (T1 disease). Pathology review of colorectal cancers should include testing for mismatch repair proteins for all patients. Tumors of patients with metastatic colorectal cancer should also be tested for extended RAS and BRAF mutations.

Following surgical resection, chemotherapy has been demonstrated to improve overall and tumor-free survival in select patients with colon cancer depending on stage (Table 39–2).

1. Stage I—Because of the excellent 5-year survival rate (approximately 92%), no adjuvant therapy is recommended for stage I colon cancer.

2. Stage II (node-negative disease)—The 5-year survival rate is approximately 87% for stage IIA disease and 63% for stage IIB disease. A significant survival benefit from adjuvant chemotherapy has not been demonstrated in most randomized clinical trials for stage II colon cancer (see discussion for stage III disease). However, otherwise healthy patients with stage II disease who are at higher risk for recurrence (perforation; obstruction; close or indeterminate margins; poorly differentiated histology; lymphatic, vascular, or perineural invasion; T4 tumors; or fewer than 12 lymph nodes sampled) may benefit from adjuvant chemotherapy. Patients whose tumors reveal MSI have a more favorable prognosis and do not benefit from 5-fluorouracil-based adjuvant therapy.

3. Stage III (node-positive disease)—With surgical resection alone, the expected 5-year survival rate is 30–50%. Postoperative adjuvant chemotherapy significantly increases disease-free survival as well as overall survival by up to 30% and is recommended for all fit patients (Table 39–2). Multiple large, well-designed studies of adjuvant therapy for stage III colorectal cancer have reported a higher rate of disease-free survival at 5 years for patients treated for 6 months postoperatively with a combination of oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) (73.3%) than with 5-fluorouracil and leucovorin (FL) alone (67.4%). Similar benefit was reported for patients treated with oxaliplatin and capecitabine (orally active fluoropyrimidine). A large international randomized controlled trial comparing 3 months with 6 months of adjuvant therapy for colon cancer found that 3 months of adjuvant therapy resulted in equivalent disease-free survival for patients with earlier stage T1, T2, or T3, and N1 disease but not with more advanced T4 or N2 disease. For patients with high-risk disease (T4 or N2), 6 months of adjuvant chemotherapy are still recommended. The addition of a

biologic agent (bevacizumab or cetuximab) to adjuvant chemotherapy does not improve outcomes.

4. Stage IV (metastatic disease)—Approximately 20% of patients have metastatic disease at the time of initial diagnosis, and an additional 30% eventually develop metastasis. A subset of these patients has limited disease that is potentially curable with surgical resection. Surgery may also be warranted to provide palliation of tumor bleeding or obstruction. Resection of isolated liver metastases may result in long-term (over 5 years) survival in 35–55% of cases. For those with unresectable hepatic metastases, local ablative techniques (cryosurgery, radiofrequency or microwave coagulation, embolization, hepatic intra-arterial chemotherapy) or radiation may provide long-term tumor control. A subset of patients who have isolated pulmonary metastases may undergo resection or radiation with potential cure. In the absence of other treatment, the median survival is less than 12 months; however, with current therapies, median survival approaches 30 months. Primary cancer location has been found to have a potential prognostic importance: median survival times are 33.3 months for patients with left-sided colon cancers compared to 19.4 months for those with right-sided cancers.

The goals of therapy for patients with metastatic colorectal cancer are to slow tumor progression while maintaining a reasonable quality of life for as long as possible. Currently, either FOLFOX (the addition of oxaliplatin to 5-fluorouracil and folinic acid) or FOLFIRI (the addition of irinotecan to 5-fluorouracil and folinic acid) is the preferred first-line treatment regimen for fit patients. For convenience, oral capecitabine (instead of intravenous 5-fluorouracil and leucovorin) can be used in combination with oxaliplatin since it has similar efficacy to 5-fluorouracil; however, combination with irinotecan is not recommended due to increased toxicity (diarrhea). Addition of a biologic agent to combination chemotherapy improves response rates and overall survival and is recommended in the first line of treatment in suitable patients. Bevacizumab is a monoclonal antibody targeting VEGF. Combination of bevacizumab with FOLFOX or FOLFIRI prolongs mean survival by 2–5 months compared with either regimen alone. Cetuximab and panitumumab are monoclonal antibodies targeting EGFR. Activating *K-ras* gene mutations downstream of EGFR are present in approximately 35% of patients with metastatic colorectal cancer and are a biomarker for nonresponse to cetuximab and panitumumab, for which reason the use of these agents is restricted to patients with tumors wild-type for *K-ras*. Mutations in *N-ras* and *BRAF* are also predictive of nonresponse to EGFR inhibition alone. In stage IV patients with *K-ras* wild-type cancers, the addition of panitumumab or cetuximab to FOLFOX or FOLFIRI prolongs survival by approximately 4 months.

When disease progresses despite treatment either with FOLFOX or with FOLFIRI (often in conjunction with bevacizumab or an EGFR-targeted antibody), therapy is switched to the alternate regimen. Although the ideal sequence of agents is not known, patients do benefit from exposure to all available therapies. Clinical trial participation should be considered for eligible patients who are

intolerant of or ineligible for standard therapies or in whom disease has progressed.

B. Rectal Cancer

The treatment approach to rectal cancer is guided by clinical staging as determined by colonoscopy and endorectal ultrasound or MRI with endorectal coil. In carefully selected patients with small (less than 4 cm), mobile, well-differentiated T1 rectal cancers that are less than 8 cm from the anal verge, transanal endoscopic or surgical excision may be considered. All other patients with rectal cancer require either a low anterior resection with a colorectal anastomosis or an abdominoperitoneal resection with a colostomy, depending on how far above the anal verge the cancer is located and the extent of local tumor spread.

For invasive rectal carcinoma, preoperative (neoadjuvant) therapy with radiation or chemoradiation, with or without postoperative (adjuvant) therapy with chemotherapy or chemoradiation, is generally recommended in all node-positive tumors and in T3 and greater tumors due to increased risk of local recurrence. The choice and timing of radiation and chemotherapy depend on a host of factors. Neoadjuvant chemoradiation has become the preferred standard in many centers because chemotherapy is more tolerable prior to surgery, leads to improved local control, and may result in improved long-term survival. For patients with clinical node-positive disease, a bulky primary cancer (T4), or a low-lying cancer that will require a permanent colostomy, giving all chemotherapy in the neoadjuvant setting (total neoadjuvant therapy) is now an option in NCCN guidelines.

After neoadjuvant therapy, the operative approach (low anterior resection versus abdominoperitoneal resection with colostomy) depends on how far above the anal verge the cancer is located, its size and depth of penetration, and the patient's overall condition. Careful dissection of the entire mesorectum by either open or laparoscopic surgery reduces local recurrence to 5%. Although low anterior resections obviate a colostomy, they are associated with increased immediate postsurgical complications (eg, leak, dehiscence, stricture) and long-term defecatory complaints (eg, increased stool frequency, and incontinence). With unresectable rectal cancer, the patient may be palliated with a diverting colostomy.

► Follow-Up After Surgery

Colorectal cancer patients who have undergone resections for cure are monitored closely to look for evidence of symptomatic or asymptomatic tumor recurrence that may occasionally be amenable to curative resection. Patients should be evaluated every 3–6 months for 2 years and then every 6 months for a total of 5 years with history, physical examination, and laboratory surveillance, including serum CEA levels if baseline levels are elevated. The NCCN and ASCO guidelines recommend surveillance contrast CT scans of chest, abdomen, and pelvis up to every 6–12 months for up to 5 years post-resection in high-risk stage II and all stage III patients. Patients who had a

complete preoperative colonoscopy should undergo another colonoscopy 1 year after surgical resection. Patients who did not undergo full colonoscopy preoperatively also should undergo a full colonoscopy after completion of all adjuvant therapy to exclude other synchronous colorectal neoplasms. If a colonoscopy does not detect new adenomatous polyps 1 year postoperatively, surveillance colonoscopy should be performed every 3–5 years thereafter to look for metachronous polyps or cancer. New onset of symptoms or a rising CEA warrants investigation with chest, abdominal, and pelvic CT and colonoscopy to look for a new primary tumor or recurrence, or metachronous metastatic disease that may be amenable to curative or palliative therapy. The majority of colorectal cancer recurrences occur within 3 years of the conclusion of treatment, and almost all (greater than 90%) occur within 5 years.

► Prognosis

The stage of disease at presentation remains the most important determinant of 5-year survival in colorectal cancer, which is estimated in older registries as: stage I, greater than 90%; stage II, 70–85%; stage III with fewer than 4 positive lymph nodes, 67%; stage III with more than 4 positive lymph nodes, 33%; and stage IV, 5–7%. Long-term registry follow-up data from the modern chemotherapy era are not yet available. For each stage, rectal cancers have a worse prognosis. For those patients whose disease progresses despite therapy, meticulous efforts at palliative care are essential (see Chapter 5).

► Screening for Colorectal Neoplasms

Colorectal cancer is ideal for screening because it is a common disease that is fatal in almost 50% of cases and yet is curable if detected at an earlier stage. Furthermore, most cases arise from benign adenomatous or serrated polyps that progress over many years to cancer, and removal of these polyps has been shown to prevent the majority of cancers. Colorectal cancer screening is endorsed by the USPSTF, the Agency for Health Care Policy and Research, the American Cancer Society, and every professional gastroenterology and colorectal surgery society. Although there is continued debate about the optimal cost-effective means of providing population screening, there is now almost unanimous consent that screening of some kind should be offered to all adults ages 45–75 years. The 2018 American Cancer Society recommendations for screening and 2020 USPSTF draft recommendations for screening are listed in Table 39–6. Due to a rising incidence of colorectal cancer in adults younger than 50 years, the 2020 USPSTF and 2018 American Cancer Society guidelines both endorse consideration of screening in asymptomatic, average-risk adults beginning at age 45; however, the cost-effectiveness of this strategy is uncertain. It is important for primary care providers to understand the relative merits of various options and to discuss them with their patients.

The potential for harm from screening must be weighed against the likelihood of benefit, especially in elderly patients with comorbid illnesses and shorter life expectancy. Although routine screening is not recommended in

Table 39–6. Recommendations for colorectal cancer screening,¹ based on updated draft 2020 US Preventive Services Task Force and 2018 American Cancer Society recommendations.²

Average-risk individuals ≥ 45 years old ²
Annual fecal occult blood testing using higher sensitivity tests (Hemoccult SENSA)
Annual fecal immunochemical test (FIT)
Fecal DNA test (interval uncertain)
Flexible sigmoidoscopy every 5 years
Colonoscopy every 10 years
CT colonography every 5 years
Individuals with a family history of a first-degree member with colorectal neoplasia ³
Single first-degree relative with colorectal cancer diagnosed at age 60 years or older: Begin screening at age 40. Screening guidelines same as average-risk individual; however, preferred method is colonoscopy every 10 years.
Single first-degree relative with colorectal cancer or advanced adenoma diagnosed before age 60 years, or two first-degree relatives: Begin screening at age 40 or at age 10 years younger than age at diagnosis of the youngest affected relative, whichever is first in time. Recommended screening: colonoscopy every 5 years.

¹For recommendations for families with inherited polyposis syndromes or hereditary nonpolyposis colon cancer, see Chapter 15.

²The American Cancer Society recommends screening of average-risk adults from age 45 to 75; the US Preventive Services Task Force recommends screening of all adults ages 50–75 (Grade A recommendation) and ages 45–59 (Grade B). Both recommend screening in selected patients ages 76–85 based on life expectancy, patient preferences, overall health, and prior screening results.

adults above age 75, it may be considered on a case-by-case basis in adults age 76 through 85 years who have excellent health and functional status.

Patients with first-degree relatives with colorectal neoplasms (cancer or adenomatous polyps) are at increased risk. Therefore, most guidelines recommend initiating screening at age 40–50 years (or 10 years younger than the familial diagnosis) in individuals with first-degree relatives with colorectal cancer or with advanced adenomas. Recommendations for screening in families with inherited cancer syndromes or inflammatory bowel disease are provided in Chapter 15.

Screening tests may be classified into two broad categories: stool-based tests and examinations that visualize the structure of the colon by direct endoscopic inspection or radiographic imaging.

A. Stool-Based Tests

1. Fecal occult blood test—Most colorectal cancers and some large adenomas result in increased chronic blood loss. A variety of tests for fecal occult blood are commercially available that have varying sensitivities and specificities for colorectal neoplasia. These include guaiac-based fecal occult blood tests (gFOBT) (eg, Hemoccult I and II and Hemoccult SENSA) that detect the pseudoperoxidase activity of heme or hemoglobin and fecal immunochemical tests (FITs) that detect human globin. In clinical trials, FITs

have proven superior to gFOBT in sensitivity for detection of colorectal cancer and advanced adenomas with similar specificity. Because FITs are not affected by diet or medications and have superior accuracy, the USMSTF now recommends their use instead of gFOBT. In 19 clinical studies, the pooled sensitivity and specificity of FIT for colorectal cancer in average-risk patients were 79% and 94%, respectively.

FIT testing is the preferred option for population-based screening in various European and Australian programs. In the United States, it is offered as the preferred option by many health care plans. For health care systems in which screening colonoscopy is readily available, FIT is a suitable option for patients seeking a noninvasive screening test who are willing to undertake annual fecal testing. The optimal interval (yearly or every 2 years) and number of stool samples (one or two) required for optimal FIT testing is as yet undetermined, but currently annual testing is recommended. Patients with a positive FIT test must undergo further evaluation with colonoscopy.

2. Multitarget DNA assay—Stool DNA tests measure a variety of mutated genes and methylated gene markers from exfoliated tumor cells. A newer-generation assay (Cologuard) combines a fecal DNA panel with a FIT. In a prospective comparative trial conducted in persons at average risk for colorectal cancer undergoing colonoscopy, the sensitivity for colorectal cancer for Cologuard was 92.3% vs 73.8% for FIT alone and the sensitivity for adenomas larger than 1 cm or serrated polyps for Cologuard was 42.4% vs 23.8% for FIT alone. A positive stool DNA test requires colonoscopy evaluation. Compared with FIT testing alone, FIT-fecal DNA testing has disadvantages including higher cost, lower specificity, lower cost-effectiveness, and cumbersome requirements for stool collection and mailing.

B. Endoscopic Examinations of the Colon

1. Colonoscopy—Colonoscopy permits examination of the entire colon. In addition to detecting early cancers, colonoscopy allows removal of adenomatous polyps by biopsy or polypectomy, which is believed to reduce the risk of subsequent cancer. Over the past decade, there has been a dramatic increase in screening colonoscopy, with over 60% of US adults screened in the past 10 years. In asymptomatic individuals between 50 and 75 years of age undergoing screening colonoscopy, the prevalence of advanced colonic neoplasia is 4–11% and of colon cancer is 0.1–1%.

Although colonoscopy is believed to be the most sensitive test for detecting adenomas and cancer, it has several disadvantages. Adequate visualization of the entire colonic mucosa requires thorough bowel cleansing the evening and morning prior to the examination. To alleviate discomfort during the procedure, intravenous sedation is used for most patients, necessitating a companion to transport the patient home post-procedure. Serious complications occur uncommonly; they include perforation (0.1%), bleeding (0.25%), and death (2.9/100,000).

The skill of the operator has a major impact upon the quality of the colonoscopy examination. In several studies, the rate of colorectal cancer within 3 years of a screening

colonoscopy was 0.7–0.9%, ie, approximately 1 in 110 patients. Population-based case-control and cohort studies suggest that colonoscopy is associated with greater reduction in colorectal cancer incidence and mortality in the distal colon (80%) than the proximal colon (40–60%). This may be attributable to incomplete examination of the proximal colon, and differences between the proximal and distal colon that include worse bowel preparation, suboptimal colonoscopic technique, and a higher prevalence of serrated polyps and flat adenomas, which are more difficult to identify than raised (sessile or pedunculated) polyps. To optimize diagnostic accuracy as well as patient safety and comfort, colonoscopy should be performed after optimal bowel preparation by a well-trained endoscopist who spends sufficient time (at least 7 minutes) carefully examining the colon (especially the proximal colon) while withdrawing the endoscope.

2. Flexible sigmoidoscopy—Use of a 60-cm flexible sigmoidoscope permits visualization of the rectosigmoid and descending colon. Adenomatous polyps are identified in 10–20% and colorectal cancers in 1% of patients. The finding at sigmoidoscopy of an adenomatous polyp in the distal colon increases the likelihood at least twofold that an advanced neoplasm is present in the proximal colon.

The chief disadvantage of screening with flexible sigmoidoscopy is that it requires some bowel cleansing, it may be associated with some discomfort (since intravenous sedation is not used), and it does not examine the proximal colon. The prevalence of proximal versus distal neoplasia is higher in persons older than age 65 years, in Blacks, and in women.

C. Radiographic and Other Imaging of the Colon

1. CT colonography—CT colonography requires a similar bowel cleansing regimen as colonoscopy as well as insufflation of air into the colon through a rectal tube, which may be associated with discomfort. Using current imaging software with multidetector helical scanners, the sensitivity is greater than 95% for the detection of cancer and greater than 84–92% for the detection of polyps 10 mm or larger. CT colonography is less sensitive than colonoscopy for the detection of polyps smaller than 1 cm, flat adenomas, and serrated polyps.

The chief disadvantages of CT colonography are the need for a bowel preparation, limited availability in many health care systems, a possible increased risk of neoplasia due to radiation exposure, and the potential for finding incidental extracolonic findings that may lead to further evaluations. CT colonography is an excellent screening option in patients who do not wish to undergo or are unsuitable for colonoscopy and in patients in whom colonoscopy could not be completed.

2. Capsule colonoscopy—Imaging of the colon can be accomplished by oral ingestion of a capsule that captures video images of the colon. Compared with colonoscopy, the colon capsule has reduced sensitivity for polyps greater than 6 mm (64% vs 84%) and for colorectal cancers (74% vs 100%). At present, it is approved by the FDA for

evaluation in patients who are not suitable candidates for colonoscopy or in whom colonoscopy could not evaluate the proximal colon. In addition to its suboptimal sensitivity for neoplasia, the main disadvantages of capsule colonoscopy are its cost, need for extensive bowel preparation, lack of reimbursement by most insurance carriers, and small risk of small bowel obstruction.

► When to Refer

- Patients with symptoms (change in bowel habits, hematochezia), signs (mass on abdominal examination or digital rectal examination), or laboratory tests (iron deficiency anemia) suggestive of colorectal neoplasia should be referred for colonoscopy.
- Patients with suspected colorectal cancer or adenomatous polyps of any size should be referred for colonoscopy.
- Virtually all patients with proven colorectal cancer should be referred to a surgeon for resection. Patients with clinical stage T3 or node-positive rectal tumors (or both) also should be referred to medical and radiation oncologists preoperatively for neoadjuvant therapy. Patients with stage II, III, or IV colorectal tumors should be referred to a medical oncologist.

► When to Admit

- Patients with complications of colorectal cancer (obstruction, acute bleeding) requiring urgent evaluation and intervention.
- Patients with advanced metastatic disease requiring palliative care.

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CARCINOMA OF THE ANUS

The anal canal is lined from its proximal to distal extent by columnar, transitional, and non-keratinized squamous epithelium, which merges at the anal verge with the keratinized perianal skin. Cancers arising from the mucosa of the anal canal are relatively rare, comprising only 1–2% of all cancers of the anus and large intestine. Squamous cancers make up the majority of anal cancers. Anal cancer is increased among people practicing receptive anal intercourse and those with a history of anorectal warts. In over 80% of cases, HPV may be detected, suggesting that this virus is a major causal factor. In a large controlled trial, HPV vaccination of healthy men (16 to 26 years old) who have sex with men decreased the incidence of anal intraepithelial neoplasia by 50%. Women with anal cancer are at increased risk for cervical cancer (which may be due to a field effect of oncogenic HPV infection) and require gynecologic screening and monitoring. Anal cancer is increased in HIV-infected individuals, possibly due to interaction with HPV. Nine-valent HPV (9vHPV) vaccine is recommended for boys and girls starting at age 11 or 12 and for individuals up to age 26 who have not been previously vaccinated. Thereafter, shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated.

Bleeding, pain, and local mass are the most common symptoms. The lesion is often confused with hemorrhoids or other common anal disorders. These tumors tend to become annular, invade the sphincter, and spread upward via the lymphatics into the perirectal mesenteric lymphatic nodes. CT or MRI scans of the abdomen and pelvis are required to identify regional lymphadenopathy or metastatic disease at diagnosis. PET imaging may be used in conjunction.

Treatment depends on the tumor location and histologic stage. Well-differentiated and small (less than 2 cm) superficial lesions of the perianal skin may be treated with wide local excision.

Adenocarcinoma of the anal canal is treated in similar fashion to rectal cancer (see above), commonly by abdominoperineal resection with neoadjuvant chemoradiotherapy and adjuvant chemotherapy. The more common **squamous cell cancer of the anal canal** and large perianal tumors invading the sphincter or rectum are treated with combined-modality therapy that includes external radiation with simultaneous chemotherapy (5-fluorouracil plus mitomycin). Local control is achieved in approximately 80% of patients. Radical surgery (abdominoperineal resection) is reserved for patients who fail chemotherapy and radiation therapy. Metastatic disease is generally treated with carboplatin and paclitaxel. The 5-year survival rate is 81% for localized tumors and approximately 30% for metastatic (stage IV) disease.

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CANCERS OF THE GENITOURINARY TRACT

George R. Schade, MD

PROSTATE CANCER



ESSENTIALS OF DIAGNOSIS

- ▶ Prostatic induration on digital rectal examination (DRE) or elevation of PSA.
- ▶ Most often asymptomatic.
- ▶ Rarely: systemic symptoms (weight loss, bone pain).

► General Considerations

Prostate cancer is the most common noncutaneous cancer and the second leading cause of cancer-related death in American men with an estimated 191,930 new prostate cancer diagnoses and 33,330 prostate cancer deaths in 2020. The clinical incidence, however, does not match the prevalence of the disease. Autopsy studies have demonstrated that more than 40% of men over age 50 years have prostate cancer, and its prevalence increases with age with 30% of men aged 60–69 years and 67% of men aged 80–89 years harboring the disease at autopsy. Most of these occult cancers are small indolent organ-confined cancers with few representing regional or metastatic disease. Although the global prevalence of prostatic cancer at autopsy is relatively consistent, the clinical incidence varies considerably (high in North America and European countries, intermediate in South America, and low in the Far East). A 50-year-old American man has a lifetime risk of 40% for latent cancer, a 16% risk for developing clinically apparent cancer, and a 2.9% risk of death due to prostatic cancer. Black race, family history of prostatic cancer, and history of high dietary fat intake are risk factors for prostate cancer.

► Clinical Findings

A. Symptoms and Signs

Presently, most prostate cancers are asymptomatic and are diagnosed because of elevations in serum PSA. However, some men will be diagnosed based on discrete nodules or areas of induration within the prostate on a DRE. Obstructive voiding symptoms are most often due to benign prostatic hyperplasia, which occurs in the same age group. Nevertheless, large or locally extensive prostatic cancers can cause obstructive voiding symptoms, including urinary

retention. Lymph node metastases can lead to lower extremity lymphedema. Because the axial skeleton is the most common site of metastases, patients may present with back pain, pathologic fractures, or rarely neurologic symptoms from epidural metastases and cord compression.

B. Laboratory Findings

1. Serum tumor markers—PSA is a glycoprotein produced only by prostatic cells, either benign or malignant. The serum level is typically low and correlates with the total volume of prostate tissue and tends to increase with age. Measurement of serum PSA is useful in detecting and staging prostate cancer, monitoring response to treatment, and identifying recurrence before it becomes clinically evident. As a screening test, PSA is elevated (greater than 4.0 ng/mL [4.0 mcg/L]) in 10–15% of men. Prostate cancer will be diagnosed in approximately 18–30% of men with PSA 4.1–10 ng/mL (4.1–10 mcg/L) and 50–70% of men with PSA greater than 10 ng/mL (10 mcg/L). However, no PSA threshold excludes the diagnosis of prostate cancer.

In untreated patients with prostate cancer, the level of PSA correlates with the volume and stage of disease. Patients with PSA levels less than 10 ng/mL (10 mcg/L) usually have localized and therefore potentially curable cancers, while those with PSA levels in excess of 40 ng/mL (40 mcg/L) are more likely to have advanced disease (seminal vesicle invasion, lymph node involvement, or occult distant metastases). Approximately 98% of patients with metastatic prostate cancer will have an elevated PSA level. However, there are rare cancers that are localized despite substantial elevations in PSA. Therefore, initial treatment decisions cannot be made on the basis of PSA testing alone. A rising PSA after therapy is usually consistent with progressive disease, either locally recurrent or metastatic.

2. Miscellaneous laboratory testing—Patients with urinary retention or with ureteral obstruction due to locoregionally advanced prostate cancers may present with elevations in blood urea nitrogen or serum creatinine. Patients with bony metastases may have elevations in serum alkaline phosphatase or calcium. Laboratory and clinical evidence of disseminated intravascular coagulation can occur in patients with advanced prostate cancers.

3. Prostate biopsy—Transrectal ultrasound-guided biopsy is the standard method for detection of prostate cancer. The use of a spring-loaded, 18-gauge biopsy needle has allowed transrectal biopsy to be performed with minimal patient discomfort and morbidity. Local anesthesia is standard and increases the tolerability of the procedure. The specimen preserves glandular architecture and permits accurate grading. Prostate biopsy specimens are taken from the apex, mid-portion, and base in men who have an abnormal DRE or an elevated serum PSA, or both. Extended-pattern biopsies, including a total of at least 10 biopsies, are associated with improved cancer detection and risk stratification of patients with newly diagnosed disease. In addition, suspicious hypoechoic prostatic lesions seen on transrectal ultrasound may be targeted for biopsy. Patients with abnormalities of the seminal vesicles can have these structures specifically biopsied to identify local tumor invasion.

C. Imaging

Use of imaging for staging should be tailored to the likelihood of advanced disease in newly diagnosed cases. CT of the abdomen and pelvis and **radionuclide (99-technetium) bone scans** are generally the first-line staging studies performed, when indicated, to assess for nodal and bony metastases, respectively.

MRI allows for evaluation of the prostate as well as regional lymph nodes. The positive predictive value for detection of both capsular penetration and seminal vesicle invasion is similar for transrectal ultrasound and MRI, although newer **multi-parametric MRI** techniques may better stage patients considering treatment or, alternatively, active surveillance. Additionally, there is a growing role for multi-parametric MRI in prostate cancer diagnosis, particularly among men with previous negative prostate biopsies, to evaluate for suspicious prostatic lesions. Such lesions may then be sampled via MRI-guided needle biopsy or via MR Fusion (in which prostate MRI images are fused in real-time with images from an ultrasound-guided needle biopsy). Such an approach may improve not only overall cancer detection but discovery of clinically relevant disease, and its use in routine clinical practice has increased and continues to evolve.

Conventional **radionuclide (99-technetium) bone scans** are superior to conventional plain skeletal radiographs in detecting bony metastases. Prostate cancer bony metastases tend to be multiple and most commonly occur in the axial skeleton. Men with more advanced local lesions, symptoms of metastases (eg, bone pain), high-grade disease, or elevations in PSA greater than 20 ng/mL (20 mcg/L) should undergo radionuclide bone scan. **PET** (eg, ¹⁸F-sodium fluoride [¹⁸F-NaF] PET) and ¹⁸F-NaF **PET/CT hybrid imaging** are more sensitive than conventional bone scans. However, a high frequency of abnormal scans with ¹⁸F-NaF PET/CT resulting from degenerative joint disease has limited their usefulness. **Fluciclovine (Axumin) PET imaging** has been approved for suspected cancer recurrence based on elevated PSA after prior treatment. **PSMA (prostate-specific membrane antigen) PET**, using small-molecule radiotracers targeting PSMA (eg, ¹⁸F-DCFBC [N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-¹⁸F-fluorobenzyl-L-cysteine]) has shown significant promise as a next-generation imaging method and may replace traditional imaging modalities in the future.

Despite application of modern, sophisticated techniques, understaging of prostate cancer occurs in at least 20% of patients.

D. Genetic Testing

The role of genetics in prostate cancer diagnosis and management is evolving. A family history of prostate cancer increases the risk of prostate cancer. Additionally, prostate cancer has been associated with several hereditary cancer syndromes (eg, Lynch syndrome, hereditary breast and ovarian cancer syndrome, etc.) with approximately 11% of prostate cancer patients with at least one additional primary cancer carrying germline mutations. Consequently, some patients with prostate cancer and their families may have

elevated risk for other cancers. Further, data suggest that some germline mutations, such as *BRCA1/2*, are associated with lower PSA at diagnosis and increased risk of progression and death; approximately 12% of patients with metastatic prostate cancer have germline mutations in homologous DNA repair genes. Finally, germline mutations in DNA repair genes can have implications for treatment and, as a result, play a role in personalized treatment.

Patients with prostate cancer should have a thorough review of their family history and those with a concerning family history should be referred for genetic counselling and possible testing. Additionally, patients with high-risk disease or metastatic disease should undergo genetic evaluation as well.

► Screening for Prostate Cancer

The impact of prostate cancer screening on mortality remains controversial. The screening tests currently available include DRE, PSA testing, and transrectal ultrasound. Prostate cancer detection rates using DRE alone vary from 1.5% to 7%, but unfortunately, most of these cancers are advanced (stage T3 or greater). Transrectal ultrasound should not be used as a first-line screening tool due to its expense, low specificity, and minimal improvement in detection rate versus the combined use of DRE and PSA testing.

PSA testing increases the detection rate of prostate cancers compared with DRE. Approximately 2–2.5% of men older than 50 years of age will be found to have prostate cancer using PSA testing compared with a rate of approximately 1.5% using DRE alone. The sensitivity, specificity, and positive predictive value of PSA and DRE are listed in Table 39–7. PSA-detected cancers are more likely to be localized compared with those detected by DRE alone. The Prostate Cancer Prevention Trial provided data demonstrating a significant risk of prostate cancer even in men with PSA less than 4.0 ng/mL (4.0 mcg/L) (Table 39–8) and a web-based calculator has been developed to estimate the risk of harboring both prostate cancer and high-grade cancer (<http://riskcalc.org/PBCG>).

Table 39–7. Screening for prostatic cancer: test performance.

Test	Sensitivity	Specificity	Positive Predictive Value
Abnormal PSA (> 4 ng/mL [mcg/L])	0.67	0.97	0.43
Abnormal DRE	0.50	0.94	0.24
Abnormal PSA or DRE	0.84	0.92	0.28
Abnormal PSA and DRE	0.34	0.995	0.49

DRE, digital rectal examination; PSA, prostate-specific antigen. Modified, with permission, from Kramer BS et al. Prostate cancer screening: what we know and what we need to know. Ann Intern Med. 1993;119:914. Copyright © 1993 American College of Physicians. All rights reserved.

Table 39–8. Risk of prostate cancer in men with PSA ≤ 4.0 ng/mL (or mcg/L).

PSA Level (ng/mL [or mcg/L])	Percentage with Prostate Cancer	Percentage with High-Grade ¹ Prostate Cancer
≤ 0.5	6.6	12.5
0.6–1.0	10.1	10.0
1.1–2.0	17.0	11.8
2.1–3.0	23.9	19.1
3.1–4.0	26.9	25.0

¹High-grade cancer was defined as Gleason score ≥ 7 .

Data from Thompson IM et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. *N Engl J Med*. 2004;350:2239.

To improve the performance of PSA as a screening test, several investigators have developed alternative methods for its use. These include establishment of age- and race-specific reference ranges, measurement of free serum and protein-bound levels of PSA (**percent free PSA**), and calculation of changes in PSA over time (**PSA velocity**). Generally, men with PSA free fractions exceeding 25% are unlikely to have prostate cancer, whereas those with free fractions less than 10% have an approximately 50% chance of having prostate cancer. Newer tests, including the Prostate Health Index (PHI) and 4kscore (<https://4kscore.com>), may better identify not only men at greater risk for prostate cancer but those with more aggressive disease.

The frequency of PSA testing also remains a matter of debate. The traditional yearly screening approach may not be the most efficient; rather, earlier PSA testing at younger age may allow less frequent testing later as well as provide information regarding PSA velocity. Men with PSA above the age-based median when tested between 40 and 60 years are at significantly increased risk for subsequent cancer detection over 25 years. Men aged 40–50 with PSA below 0.6 ng/mL (0.6 mcg/L) and aged 50–60 with PSA below 0.71 ng/mL (0.71 mcg/L) may require less frequent PSA tests. In addition, men with PSA velocity greater than 0.35 ng/mL (0.35 mcg/L) per year measured 10–15 years before diagnosis had significantly worse cancer-specific survival compared with those with lower PSA velocity. The NCCN guidelines (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp) for prostate cancer early detection incorporate many of these factors. The European Association of Urology (EAU) recommends offering PSA screening to men beginning at age 40–50 years, dependent on risk factors, and subsequently initiating a risk-adapted strategy.

Two large, randomized trials have evaluated the benefit of PSA screening for early detection of prostate cancer. In the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, no mortality benefit was observed after combined screening with PSA testing and DRE during 15-year follow-up. Although screening resulted in a 12% increase in prostate cancer detection, the cancer-specific mortality rate was similar in the screening and control

arms (2.55 and 2.44 deaths per 10,000 person-years, respectively). However, an estimated 86% of control patients received at least one screening PSA test and 46% of control patients received yearly PSA screening during the trial. Conversely, the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial demonstrated a significant 20% reduction in prostate cancer mortality with an absolute reduction of 1.75 deaths per 1000 men screened at 16 years. The number of men needed to be invited for screening to prevent one prostate cancer death was 570 at 16 years compared with 742 at 13 years, while the number of prostate cancers needing to be diagnosed to prevent one prostate cancer death was reduced from 26 to 18, underscoring the importance of adequate long-term follow-up for prostate cancer.

In 2018, the USPSTF issued a revised (Grade C) recommendation for men aged 55 to 69 years that the decision to undergo periodic PSA-based screening should be an individual one. Before deciding about screening, men should discuss its potential benefits and harms with their clinician, incorporating their own values and preferences in the decision. The revised recommendation acknowledges that, while screening offers some men a small potential benefit of reducing the chance of dying from prostate cancer, many other men will experience potential harms from screening. These include false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether screening is appropriate in individual cases, the individual patient's family history, race/ethnicity, comorbid medical conditions, values about the benefits and harms of screening and treatment-specific outcomes, and other health needs should be considered. Clinicians should not screen men who do not express a preference for screening. For men age 70 years and older, the USPSTF recommends against PSA-based screening (Grade D recommendation).

► Staging

The majority of prostate cancers are adenocarcinomas. Most arise in the peripheral zone of the prostate, though a small percentage arise in the central (5–10%) and transition zones (20%) of the gland. Pathologists utilize the Gleason grading system whereby a “primary” grade is applied to the architectural pattern of malignant glands occupying the largest area of the specimen and a “secondary” grade is assigned to the next largest area of cancer. Grading is based on architectural rather than histologic criteria, and five “grades” are possible. Adding the score of the primary and secondary grades gives a Gleason score from 2 to 10. Gleason score correlates with tumor volume, pathologic stage, and prognosis. A simplified five-grade group system has been introduced by the International Society of Urological Pathologists.

► Treatment

A. General Measures

The optimal management of localized prostate cancer remains controversial owing to the plethora of treatment

options, side effects of the various options, and indolent nature of many prostate cancers. These factors have contributed to uncertainty regarding a definitive survival benefit of treating localized prostate cancer. To help guide treatment decision making, patients are risk stratified according to their PSA level at diagnosis, DRE, and prostate cancer grade (Gleason score). Additionally, patients should have an assessment of life expectancy prior to treatment decision-making since all patients with low-risk disease and many with intermediate-risk disease with less than 10-year life expectancy will not benefit from treatment.

B. Active Surveillance

The goal of active surveillance is to avoid treatment in men who may never require it while recognizing and definitively treating men harboring higher-risk disease in order to balance cancer risk with the morbidity of treatment. Treatment decisions are made based on stage, PSA, and cancer grade (Gleason score) as well as the age and health of the patient. Active surveillance alone may be effective management for appropriately selected patients, typically those with low PSA, small volume, well-differentiated cancers, and life expectancy less than 10–15 years. For such patients, active surveillance involves serial PSA levels, DREs, and periodic prostate biopsies to reassess grade and extent of cancer. Endpoints for intervention in patients on active surveillance, particularly PSA changes, have not been clearly defined and surveillance regimens remain an active area of research. Nonetheless, they are increasingly accepted by patients and clinicians with contemporary series demonstrating freedom from definitive treatment in greater than half of patients at 5 years, and risk of developing metastases and suffering cancer-specific death in less than 3% and 2%, respectively, at 10 years. Active surveillance, which is distinguished from mere observation (watchful waiting), is featured prominently in the NCCN and EAU guidelines and is the preferred management in most men with very low risk prostate cancer. This approach is increasingly accepted and incorporated in routine clinical practice.

C. Radical Prostatectomy

During radical prostatectomy, the seminal vesicles, prostate, and ampullae of the vas deferens are removed. Refinements in technique have allowed preservation of urinary continence in most patients and erectile function in selected patients. Radical prostatectomy can be performed via open retropubic, transperineal, or laparoscopic (with or without robotic assistance) surgery. Local recurrence is uncommon after radical prostatectomy and related to pathologic stage. Organ-confined cancers rarely recur; however, cancers with adverse pathologic features (capsular penetration, seminal vesicle invasion) are associated with higher local (10–25%) and distant (20–50%) relapse rates.

Ideal candidates for radical prostatectomy include healthy patients with stages T1 and T2 prostate cancers. Patients with advanced local tumors (T4) or lymph node metastases are rarely candidates for prostatectomy alone, although surgery is sometimes used in combination with hormonal therapy and postoperative radiation therapy for select high-risk patients.

D. Radiation Therapy

Radiation can be delivered by a variety of techniques to the prostate and, when clinically indicated, to the pelvic lymph nodes. Conformal techniques, including three-dimensional conformal radiation, intensity modulated radiotherapy, and image-guided radiotherapy, have become the standard of care for external photon-based radiotherapy, while proton beam therapy has gained acceptance as an alternative external beam therapy that theoretically may reduce toxicities. Additionally, hypofractionated and ultra-hypofractionated (ie, stereotactic radiotherapy) regimens have shown promising short- and intermediate-term outcomes vs conventionally dosed regimens. Brachytherapy—the implantation of permanent or temporary radioactive sources (palladium, iodine, or iridium) into the prostate—can be used as monotherapy in those with low-grade or low-volume malignancies or combined with external beam radiation in patients with higher-grade or higher-volume disease. The PSA may rise after brachytherapy because of prostate inflammation and necrosis. This transient elevation (PSA bounce) should not be mistaken for recurrence and may occur up to 20 months after treatment. Patients with intermediate- and high-risk disease benefit from concomitant androgen deprivation therapy. As with surgery, the likelihood of local failure following radiation correlates with technique and cancer characteristics. The likelihood of a positive prostate biopsy more than 18 months after radiation varies between 20% and 60%. Patients with local recurrence are at an increased risk of cancer progression and cancer death compared with those who have negative biopsies. Survival of patients with localized cancers (T1, T2, and selected T3) approaches 65% at 10 years. Ambiguous target definitions, inadequate radiation doses, and understaging of the cancer may be responsible for the failure noted in some series.

E. Focal Therapy

To reduce the morbidity of localized prostate cancer treatment, there has been a growing interest in focal therapy. Focal therapy delivers energy to the prostate, destroying the tumor(s) and a margin of normal prostate tissue while avoiding collateral damage to the neurovascular bundles, external urinary sphincter, bladder, and rectum. To date, several energy sources (cryotherapy, high intensity focused ultrasound, lasers, etc) have been evaluated and several others are under development. The multifocal nature and the difficulty of localizing the prostate cancer with contemporary imaging techniques combined with the prolonged disease course, lack of clearly defined endpoints, and randomized prospective data have limited the widespread adoption of focal therapies as well as a clear understanding of which are the ideal candidates.

F. Localized Disease

Although selected patients may be candidates for active surveillance based on age or health and evidence of small-volume or well-differentiated cancers, most men with an anticipated life expectancy of longer than 10 years should be considered for treatment. Newly introduced genomic tests may provide important information to help guide

treatment decisions. Both radiation therapy and radical prostatectomy result in acceptable levels of local control. A large, prospective, randomized trial compared watchful waiting with radical prostatectomy in 695 men with clinically localized and well-differentiated to moderately differentiated cancers. Radical prostatectomy significantly reduced disease-specific mortality, overall mortality, and risks of metastasis and local progression. The relative reduction in the risk of death at 23 years was 0.56 in the prostatectomy group, with the number needed to treat to avert one death (NNT) = 8 patients; the benefit was largest in men younger than age 65 years (relative risk [RR] = 0.45) and with intermediate-risk prostate cancer (RR = 0.38). Surgery also reduced the risk of metastases in older men (RR = 0.68).

G. Locally and Regionally Advanced Disease

Patients with advanced pathologic stage or positive surgical margins are at an increased risk for local and distant tumor relapse. Due to these risks, such patients have been considered for adjuvant therapy (radiation for positive margins and seminal vesicle invasion or androgen deprivation and/or radiation for lymph node metastases). Two randomized clinical trials (EORTC 22911 and SWOG 8794) demonstrated improved progression-free and metastasis-free survival with early radiotherapy in these men, and subsequent analysis of SWOG 8794 showed improved overall survival in men receiving adjuvant radiation therapy. However, the publication of two trials comparing adjuvant radiotherapy with early-salvage therapy using contemporary radiotherapy techniques (GETUG-AFU17 and RAVES) demonstrated no difference in 5-year biochemical progression-free survival casting doubt on the benefit of adjuvant radiotherapy in the contemporary era.

H. Metastatic Disease

Since death due to prostate carcinoma is almost invariably the result of failure to control metastatic disease, research has emphasized efforts to improve control of distant disease. Most prostate carcinomas are hormone dependent and approximately 70–80% of men with metastatic prostate carcinoma will respond to various forms of androgen deprivation. **Androgen deprivation therapy** may be effective at several levels along the pituitary–gonadal axis using a variety of methods or agents (Table 39–9). Use of luteinizing hormone-releasing hormone (LHRH) agonists (leuprolide, goserelin) achieves medical castration without orchectomy and is the most common method of reducing testosterone levels. A single LHRH antagonist (degarelix) is FDA approved and has no short-term testosterone “flare” associated with LHRH agonists. Because of its rapid onset of action, **ketoconazole** should be considered in patients with advanced prostate cancer who present with spinal cord compression, bilateral ureteral obstruction, or disseminated intravascular coagulation. Although testosterone is the major circulating androgen, the adrenal gland secretes the androgens dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione. This led to the development of **abiraterone acetate** (an inhibitor of CYP17, a key enzyme in androgen synthesis) to block both testicular and adrenal androgens. Nonsteroidal

antiandrogen agents act by competitively binding the receptor for dihydrotestosterone, the intracellular androgen responsible for prostate cell growth and development. In addition to immediate side effects of androgen deprivation (sexual dysfunction and hot flashes), the chronic suppression of testosterone leads to osteoporosis and risk of fractures, cardiovascular disease and diabetes mellitus, and decreased muscle and increased fat. **Bisphosphonates** can prevent osteoporosis associated with androgen deprivation, decrease bone pain from metastases, and reduce skeletal-related events. **Denosumab**, a RANK ligand inhibitor, is approved for the prevention of skeletal-related events in patients with bone metastases from prostate cancer and also appears to delay the development of these metastases in patients with castration-resistant prostate cancer. In addition, enzalutamide definitively improves metastasis-free survival in men with nonmetastatic castrate-resistant prostate cancer and rapidly rising PSAs.

The management of advanced prostate cancer is rapidly evolving. Contemporary management consists of initiating androgen deprivation therapy with orchectomy, LHRH agonist, or LHRH antagonist. A meta-analysis compared using an LHRH agonist or orchectomy alone with an LHRH agonist or orchectomy plus an antiandrogen agent; results showed little benefit of combination therapy. However, patients at risk for disease-related symptoms (bone pain, obstructive voiding symptoms) should receive concurrent antiandrogens due to the initial elevation of serum testosterone that accompanies LHRH agonists. For patients with elevated PSAs only (indicating recurrent, but nonmetastatic, cancer), nonsteroidal antiandrogen agents may be useful. Further androgen manipulations, initiation of cytotoxic chemotherapy, and local therapy (eg, radiation) is defined by the cancer’s androgen sensitivity status. For patients with hormone-sensitive metastatic prostate cancer, the addition of systemic cytotoxic chemotherapy with **docetaxol** to androgen deprivation therapy results in improved survival compared to androgen deprivation therapy alone. Similarly, the addition, of **abiraterone acetate** plus **prednisone** to androgen deprivation therapy, results in superior survival compared to androgen deprivation therapy alone.

Patients with castrate-resistant disease or prostate cancer that demonstrates rising PSA or progression of disease despite castrate levels of serum testosterone (less than 50 ng/dL) should continue their LHRH agonist/antagonist regimen. Additional treatment options are stratified based on the presence of metastatic disease. Patients with nonmetastatic castrate-resistant disease and long PSA doubling time (longer than 10 months) can simply be observed due to their relatively indolent disease. Conversely, nonmetastatic castrate-resistant patients with short doubling times (10 months or less) have demonstrated improved metastasis-free survival with the addition of the potent nonsteroidal androgen receptor antagonists **enzalutamide**, **apalutamide**, and **darolutamide** to androgen deprivation therapy. For patients with metastatic castrate-resistant prostate cancer, docetaxol was the first cytotoxic chemotherapy agent to improve survival. **Enzalutamide** and **abiraterone** improve overall survival in men with metastatic castrate prostate cancer in both the docetaxol naïve and non-naïve setting. **Cabazitaxel** is a second-line taxane

Table 39–9. Androgen deprivation for prostatic cancer.

Level	Agent	Dose	Sequelae
Pituitary, hypothalamus	Diethylstilbestrol	1–3 mg orally daily	Gynecomastia, hot flushes, thromboembolic disease, erectile dysfunction
	LHRH agonists Leuprorelin Goserelin Triptorelin Histrelin	Daily subcutaneous injection Monthly to quarterly depot injection Monthly depot injection Annual subcutaneous implant	Erectile dysfunction, hot flushes, gynecomastia, rarely anemia
	LHRH antagonist Degarelix	240 mg subcutaneously initial dose, then 80 mg subcutaneously monthly	Hot flushes, weight gain, erectile dysfunction, increased liver tests
Adrenal	Ketoconazole	400 mg three times orally daily	Adrenal insufficiency, nausea, rash, ataxia
	Aminoglutethimide	250 mg four times orally daily	Adrenal insufficiency, nausea, rash, ataxia
	Corticosteroid Prednisone	20–40 mg orally daily	Gastrointestinal bleeding, fluid retention
	CYP17a1 inhibitor Abiraterone	1000 mg orally daily (with prednisone 5 mg orally twice daily)	Weight gain, fluid retention, hypokalemia, hypertension
Testis	Orchiectomy		Gynecomastia, hot flushes, erectile dysfunction
Prostate cell	Antiandrogens Flutamide	250 mg three times orally daily	No erectile dysfunction when used alone; nausea, diarrhea
	Bicalutamide	50 mg orally daily	Liver, cardiac, and pulmonary toxicity
	Enzalutamide	160 mg orally daily	Seizures, dizziness, asthenia
	Apalutamide	240 mg orally daily	Fatigue, leukopenia, hyperlipidemia, hyperglycemia, hyperkalemia, seizures (rare)
	Doralutamide	600 mg orally twice daily	Fatigue, extremity pain, rash
	Cytotoxic chemotherapeutic agents Docetaxel		Bone marrow, skin, pulmonary, cardiac, gastrointestinal, hepatic toxicities possible
	Cabazitaxel	75 mg/m ² intravenously once on day 1 of 21-day cycle (with prednisone 10 mg orally daily)	

LHRH, luteinizing hormone-releasing hormone.

chemotherapy that improves overall survival in men who have received docetaxel. **Sipuleucel-T**, an autologous cellular immunotherapy, is FDA approved in asymptomatic or minimally symptomatic men with metastatic castration-resistant prostate cancer. **Radium-223 dichloride** is approved for the treatment of men with castration-resistant, symptomatic bone metastases, with significant improvements in both overall survival and time to skeletal-related events (eg, fractures and spinal cord compression). Finally, patients who have undergone a genetics evaluation and are found to have specific germline or somatic mutations may benefit from personalized treatment strategies.

► Prognosis

The likelihood of success of active surveillance or treatment can be predicted using risk assessment tools that usually

combine stage, grade, PSA level, and number and extent of positive prostate biopsies. Several web-based tools are available (eg, <https://www.mskcc.org/nomograms/prostate>). Widely used nomograms include the **Kattan nomogram** and the **CAPRA nomogram**. CAPRA uses serum PSA, Gleason score, clinical stage, percent positive biopsies, and patient age in a point system to risk stratify and predict the likelihood of PSA recurrence 3 and 5 years after radical prostatectomy (Tables 39–10 and 39–11) as well as metastasis and prostate cancer-specific and overall survival. The CAPRA nomogram has been validated on large multicenter and international radical prostatectomy and radiation-treated cohorts.

The patterns of prostate cancer progression have been well defined. Small and well-differentiated cancers (Gleason grade 3) are usually confined within the prostate, whereas large-volume (greater than 4 mL) or poorly differentiated

Table 39–10. The UCSF Cancer of the Prostate Risk Assessment (CAPRA).

Variable	Level	Points
PSA (ng/mL [or mcg/L] at diagnosis)	0–6	0
	6.1–10	1
	10.1–20	2
	20.1–30	3
	> 30	4
Gleason grade, primary/secondary	1–3/1–3	0
	1–3/4–5	1
	4–5/1–5	3
T stage	T1 or T2	0
	T3a	1
% positive biopsies (biopsy cores positive divided by the number of biopsies obtained)	< 34%	0
	≥ 34%	1
Age	< 50 years	0
	≥ 50 years	1

Source: <https://urology.ucsf.edu/research/cancer/prostate-cancer-risk-assessment-and-the-ucsf-capra-score>.

(Gleason grades 4 and 5) cancers are more often locally extensive or metastatic to regional lymph nodes or bone. Penetration of the prostate capsule by cancer is common and occurs along perineural spaces. Seminal vesicle invasion is associated with a high likelihood of regional or distant disease and disease recurrence. The most common sites of lymph node metastases are the obturator and internal iliac lymph node chains and of distant metastases, the axial skeleton.

Table 39–11. CAPRA: Probability of freedom from PSA recurrence after radical prostatectomy by CAPRA point total.

CAPRA Score	3-Year Recurrence-Free Survival (%) (95% CI)	5-Year Recurrence-Free Survival (%) (95% CI)
0–1	91 (85–95)	85 (73–92)
2	89 (83–94)	81 (69–89)
3	81 (73–87)	66 (54–76)
4	81 (69–89)	59 (40–74)
5	69 (51–82)	60 (37–77)
6	54 (27–75)	34 (12–57)
7+	24 (9–43)	8 (0–28)

PSA, prostate-specific antigen.

Source: <https://urology.ucsf.edu/research/cancer/prostate-cancer-risk-assessment-and-the-ucsf-capra-score>.

► When to Refer

- Refer all patients to a urologist for management of localized disease or for active surveillance.
- For metastatic disease, medical oncology should be consulted for consideration of systemic treatments.
- Active surveillance may be appropriate in selected patients with very low-volume, low-grade prostate cancer.
- Localized disease may be managed by active surveillance, surgery, or radiation therapy.
- Locally extensive, regionally advanced, and metastatic disease often require multimodal treatment strategies.

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BLADDER CANCER



ESSENTIALS OF DIAGNOSIS

- Gross or microscopic hematuria.
- Irritative voiding symptoms.
- Positive urinary cytology in most patients.
- Filling defect within bladder noted on imaging.

► General Considerations

Bladder cancer is the second most common urologic cancer; it occurs more commonly in men than women (3.1:1), and the mean age at diagnosis is 73 years. Cigarette smoking and exposure to industrial dyes or solvents are risk factors for the disease and account for approximately 60%

and 15% of new cases, respectively. In the United States, almost all primary bladder cancers (98%) are epithelial malignancies, usually urothelial cell carcinomas (90%). Adenocarcinomas and squamous cell cancers account for approximately 2% and 7%, respectively. The latter is often associated with schistosomiasis, vesical calculi, or prolonged catheter use.

► Clinical Findings

A. Symptoms and Signs

Hematuria—gross or microscopic, chronic or intermittent—is the presenting symptom in 85–90% of patients with bladder cancer. Irritative voiding symptoms (urinary frequency and urgency) occur in a small percentage of patients as a result of the location or size of the cancer. Most patients with bladder cancer do not have signs of the disease because of its superficial nature. Abdominal masses detected on bimanual examination may be present in patients with large-volume or deeply infiltrating cancers. Hepatomegaly or palpable lymphadenopathy may be present in patients with metastatic disease, and lymphedema of the lower extremities results from locally advanced cancers or metastases to pelvic lymph nodes.

B. Laboratory Findings

Urinalysis reveals microscopic or gross hematuria in the majority of cases. On occasion, hematuria is accompanied by pyuria. Azotemia may be present in a small number of cases associated with ureteral obstruction. Anemia may occasionally be due to chronic blood loss or to bone marrow metastases. Exfoliated cells from normal and abnormal urothelium can be readily detected in voided urine specimens. Cytology can be useful to detect the disease initially or to detect its recurrence. Cytology is sensitive in detecting cancers of higher grade and stage (80–90%), but less so in detecting superficial or well-differentiated lesions (50%). There are numerous urinary tumor markers under investigation for screening or assessing recurrence, progression, prognosis, or response to therapy.

C. Imaging

Bladder cancers may be identified as masses within the bladder using ultrasound, CT, or MRI. However, the presence of cancer is confirmed by cystoscopy and biopsy, with imaging primarily used to evaluate the upper urinary tract and to stage more advanced lesions.

D. Cystourethroscopy and Biopsy

The diagnosis and staging of bladder cancers are made by cystoscopy and transurethral resection. If cystoscopy—usually performed under local anesthesia—confirms the presence of a bladder tumor, the patient is scheduled for transurethral resection under general or regional anesthesia. Random bladder and transurethral prostate biopsies are occasionally performed to detect occult disease and potentially identify patients at greater risk for cancer recurrence and progression.

► Pathology & Staging

Grading is based on cellular features: size, pleomorphism, mitotic rate, and hyperchromatism. Bladder cancer staging is based on the extent (depth) of bladder wall penetration and the presence of regional or distant metastases. Both cancer grade and stage influence the natural history of bladder cancer including local recurrence within the bladder and progression to higher-stage disease.

► Treatment

Patients with superficial non-muscle invasive cancers (Tis, Ta, T1) are treated with complete transurethral resection with selective use of a single dose intravesical chemotherapy immediately following resection. The subset of patients with carcinoma in situ (Tis) and those undergoing resection of large, high-grade, recurrent Ta lesions or T1 cancers (or both) are good candidates for additional intravesical therapy.

Patients with muscle invasive (T2+) but still localized cancers are at risk for both nodal metastases and progression and require more aggressive treatment. The gold standard treatment is neoadjuvant chemotherapy followed by radical cystectomy, which confers a survival advantage versus cystectomy alone. This is particularly important for higher-stage or bulky tumors to improve their surgical resectability. Trimodal bladder preservation therapy consisting of complete transurethral resection, sensitizing systemic chemotherapy, and external beam radiotherapy can offer similar outcomes in optimally selected patients.

A. Intravesical Therapy

Immunotherapeutic or chemotherapeutic agents delivered directly into the bladder via a urethral catheter can reduce the likelihood of recurrence in those who have undergone complete transurethral resection. Most agents are administered weekly for 6–12 weeks. Efficacy may be increased by prolonging contact time to 2 hours. The use of maintenance therapy after the initial induction regimen is beneficial. Common agents include gemcitabine, mitomycin, doxorubicin, valrubicin, and bacillus Calmette-Guérin (BCG), with the last being the only agent effective in reducing disease progression. Side effects of intravesical chemotherapy include irritative voiding symptoms and hemorrhagic cystitis. Patients in whom symptoms or infection develop from BCG may require antituberculous therapy.

B. Surgical Treatment

Although transurethral resection is the initial form of treatment for all bladder tumors (since it is diagnostic, allows for proper staging, and controls superficial cancers), muscle-invasive cancers require more aggressive treatment. Partial cystectomy can be considered in selected patients with solitary lesions at the bladder dome or those with cancer in a bladder diverticulum. Radical cystectomy in men entails removal of the bladder, prostate, seminal vesicles, and surrounding fat and peritoneal attachments and in women removal of the bladder, uterus, cervix,

urethra, anterior vaginal vault, and usually the ovaries. In women with anterior tumors, vaginal and reproductive organ-sparing surgery can be considered. Bilateral pelvic lymph node dissection is performed in all patients. Urinary diversion is performed in all. In most patients, it uses a conduit of ileum or colon. However, continent forms of diversion avoid the necessity of an external appliance; it can be considered in a significant percentage of patients.

C. Radiotherapy

External beam radiotherapy delivered in fractions over a 6- to 8-week period is generally well tolerated, but approximately 10–15% of patients will develop bladder, bowel, or rectal complications. Local recurrence is common after radiotherapy alone (30–70%) and it is therefore combined with radiosensitizing systemic chemotherapy to improve complete response and to decrease recurrence rates. Bladder-preserving chemoradiation can be offered to those patients seeking to keep their bladder and is best suited for those with solitary T2 or limited T3 tumors without ureteral obstruction. Radiation with or without chemotherapy can be offered to patients with localized cancers and to patients who are poor candidates for radical cystectomy or to patients with metastatic disease seeking palliation of local symptoms.

D. Chemotherapy

Metastatic disease is present in 15% of patients with newly diagnosed bladder cancer. Furthermore, metastases develop in up to 40% of patients within 2 years of cystectomy, including those patients who were believed to have localized disease at the time of treatment. Cisplatin-based combination chemotherapy results in partial or complete responses in 15–45% of patients (see Table 39–2) and is the preferred approach.

Combination chemotherapy has been used to decrease recurrence rates in patients treated both with surgery and with radiotherapy. Neoadjuvant chemotherapy appears to benefit all patients with muscle-invasive disease prior to planned cystectomy. Chemotherapy should also be considered before surgery in those with bulky lesions or those in whom regional metastases are suspected. Alternatively, adjuvant chemotherapy has been used after cystectomy in patients at high risk for recurrence, such as those who have lymph node involvement or extravesical local invasion.

E. Immunotherapy

The FDA has now approved several checkpoint inhibitors as immunotherapy for metastatic urothelial cancer. Approved anti-PDL-1 inhibitors include **atezolizumab**, **durvalumab**, and **avelumab** (Table 39–2). Approved anti-PD1 inhibitors include **nivolumab** and **pembrolizumab**. All are approved for second-line treatment of locally advanced or metastatic urothelial cancer that progressed during or after platinum-based chemotherapy. Additionally, atezolizumab and pembrolizumab are approved as first-line therapy in cisplatin-ineligible patients whose tumors express PD-L1 or in patients ineligible for any platinum-based chemotherapy regardless of PD-L1

expression status. Overall response rates of these agents are similar and range from 17% to 25% in locally advanced and metastatic urothelial bladder cancer.

► Prognosis

The frequency of recurrence and progression are correlated with grade. Whereas progression may be noted in few low-grade cancers (19–37%), it is common with poorly differentiated lesions (33–67%). Carcinoma *in situ* is most often found in association with papillary bladder cancers. Its presence identifies patients at increased risk for recurrence and progression.

At initial presentation, approximately 50–80% of bladder cancers are superficial: stage Ta, Tis, or T1. When properly treated, lymph node metastases and progression are uncommon in such patients and survival is excellent (81%). Five-year survival of patients with T2 and T3 disease ranges from 50% to 75% after radical cystectomy. Long-term survival for patients with metastatic disease at presentation is rare.

► When to Refer

- Refer all patients to a urologist. Hematuria often deserves evaluation with both upper urinary tract imaging and cystoscopy, particularly in a high-risk group (eg, older men).
- Refer when histologic diagnosis and staging require endoscopic resection of cancer.
- Metastatic urothelial cancer should be managed by a medical oncologist.

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CANCERS OF THE URETER & RENAL PELVIS

Cancers of the ureter and renal pelvis are rare and occur more commonly in patients who have bladder cancer, Balkan nephropathy, or Lynch syndrome, who smoke, or who have a long history of analgesic abuse. The majority are urothelial cell carcinomas. Gross or microscopic hematuria is present in most patients; flank pain secondary to bleeding and obstruction occurs less commonly. As with bladder cancers, urinary cytology is often positive in high-grade cancers. The most common signs identified at the time of CT or intravenous urography include an intraluminal filling defect, unilateral nonvisualization of the collecting

system, and hydronephrosis. Ureteral and renal pelvic tumors must be differentiated from calculi, blood clots, papillary necrosis, or inflammatory and infectious lesions. On occasion, upper urinary tract lesions are accessible for biopsy, fulguration, or resection using a ureteroscope. Treatment is based on the site, size, grade, depth of penetration, and number of cancers present. Most are excised with laparoscopic or open nephroureterectomy (renal pelvic and upper ureteral lesions) or segmental excision of the ureter (distal ureteral lesions). Endoscopic resection may be indicated in patients with limited renal function or focal, low-grade, cancers. Similar to urothelial bladder cancers, use of chemotherapy prior to surgery may improve outcomes.

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RENAL CELL CARCINOMA



ESSENTIALS OF DIAGNOSIS

- ▶ Gross or microscopic hematuria.
- ▶ Flank pain or mass in some patients.
- ▶ Systemic symptoms such as fever, weight loss may be prominent.
- ▶ Solid renal mass on imaging.

General Considerations

Kidney (renal cell) and renal pelvis carcinomas account for 3.8% of all adult cancers. In 2019 in the United States, it is estimated that approximately 73,820 cases of renal cell carcinoma will be diagnosed and 14,770 deaths will result. Renal cell carcinoma has a peak incidence in the sixth decade of life and a male-to-female ratio of 2:1. It may be associated with a number of paraneoplastic syndromes.

Risk factors include physical inactivity, obesity, and diabetes mellitus. Cigarette smoking is the only known significant environmental risk factor. Familial causes of renal cell carcinoma have been identified (von Hippel-Lindau syndrome, hereditary papillary renal cell carcinoma, hereditary leiomyoma-renal cell carcinoma, and Birt-Hogg-Dubé syndrome). There is an association with dialysis-related acquired cystic disease and specific genetic aberrations (eg, Xp11.2 translocation). But sporadic carcinomas are far more common.

Renal cell carcinoma originates from the proximal tubule cells. Various histologic cell types are recognized (clear cell, papillary, chromophobe, collecting duct, and sarcomatoid).

Clinical Findings

A. Symptoms and Signs

Historically, 60% of patients presented with gross or microscopic hematuria. Flank pain or an abdominal mass was detected in approximately 30% of cases. The triad of flank pain, hematuria, and mass, found in only 10% of patients, is often a sign of advanced disease. Fever can occur as a paraneoplastic symptom. Symptoms of metastatic disease (cough, bone pain) occur in 20–30% of patients at presentation. Due to the widespread use of ultrasound and cross-sectional imaging, renal tumors are frequently detected incidentally in individuals with no urologic symptoms. Consequently, there has been profound stage migration toward lower stages of disease over the last 20 years. However, population mortality rates have remained stable.

B. Laboratory Findings

Contemporary studies suggest hematuria is present in less than 50% of patients. Erythrocytosis from increased erythropoietin production occurs in 5%, though anemia is more common; hypercalcemia may be present in up to 10% of patients. **Stauffer syndrome** is a reversible syndrome of hepatic dysfunction (with elevated liver tests) in the absence of metastatic disease.

C. Imaging

Solid renal masses are often first identified by abdominal ultrasonography or CT. CT and MRI scanning are the most valuable imaging tests for renal cell carcinoma. These scans confirm the character of the mass and provide valuable staging information with respect to regional lymph nodes, renal vein or vena cava tumor thrombus, and adrenal or liver metastases. CT and MRI also provide valuable information regarding the contralateral kidney (function, bilaterality of neoplasm). Chest radiographs or CT exclude pulmonary metastases. Bone scans should be performed for large tumors and in patients with bone pain or elevated serum alkaline phosphatase levels. Brain imaging should be obtained in patients with high metastatic burden or in those with neurologic deficits.

Differential Diagnosis

Solid renal masses are renal cell carcinoma until proven otherwise. Other solid masses include renal angiomyolipomas (fat density usually detectable by CT), renal pelvis urothelial cancers (more central location, involvement of the collecting system, positive urinary cytology), renal oncocyctomas (indistinguishable from renal cell carcinoma preoperatively), renal abscesses, and adrenal tumors (superior to the kidney).

Treatment

Surgical extirpation is the primary treatment for localized renal cell carcinoma. Patients with a single kidney, bilateral lesions, or significant medical renal disease should be considered for partial nephrectomy. Patients harboring a small tumor with a normal contralateral kidney and good kidney

function are also candidates for partial nephrectomy, while radical nephrectomy is indicated in patients with cancers larger than 7 cm and those in whom partial nephrectomy is not technically feasible. Radiofrequency and cryosurgical ablation are alternative options instead of surgery in select patients with tumors less than 3–4 cm with similar risk of metastatic progression but higher risk of local recurrence. Active surveillance is warranted in select patients (significant comorbidity, short life expectancy) and appears safe with low risk of 5-year systemic progression. Percutaneous biopsy can provide tumor histology and grade to help guide treatment decisions.

Cytotoxic chemotherapy has no role in the treatment of metastatic renal cell carcinoma. Historically, cytokine-based immunotherapies, such as interferon-alpha and interleukin-2, produced partial response rates of 15–20% and 15–35%, respectively (Table 39–2). Responders tended to have lower tumor burden, metastatic disease confined to the lung, and a high-performance status. Two randomized trials demonstrating a survival benefit of cytoreductive nephrectomy followed by systemic interferon-alpha compared with the use of systemic therapy alone led to the widespread adoption of cytoreductive nephrectomy. Patients most likely to benefit from cytoreduction were those with good performance status, lung only metastases, and good prognostic features.

Presently, management strategies are based on tumor histology and patient risk (favorable, intermediate, or poor). Several targeted medications, specifically VEGF, Raf-kinase, and mTOR inhibitors, are effective (40–60% response rates) in patients with advanced kidney cancer (Table 39–2). These oral agents, which include **sunitinib**, **pazopanib**, **cabozantinib**, **axitinib**, and **sorafenib**, are generally well tolerated and particularly active for clear cell carcinoma. The optimal timing and combination of these agents remain to be determined. Sunitinib is approved for adjuvant use after complete surgical resection in patients with adverse pathologic features. The mTOR inhibitors **everolimus** and **temsirolimus** are approved for use in patients with prior anti-VEGF therapy, as is the combination of lenvatinib and everolimus. Nivolumab is an approved anti-PD-1 immunotherapy for treating metastatic disease that has progressed despite antiangiogenic therapy. **Nivolumab** in combination with the anti-CTLA4 immunotherapy **ipilimumab** and **pembrolizumab** (anti-PD-1) in combination with the VEGF inhibitor **axitinib** have proved superior to **sunitinib** in previously untreated intermediate- and poor-risk metastatic clear cell renal cell carcinoma and are considered the standard first-line treatment for this patient population (Table 39–2).

The utilization of cytoreductive nephrectomy in combination with contemporary agents has decreased in response to the results of CARMENA and adoption of combination immunotherapy regimens (nivolumab plus ipilimumab, pembrolizumab plus axitinib). Still, there remains a role for cytoreductive surgery in select patients with intermediate-risk disease.

► Prognosis

After radical or partial nephrectomy, tumors confined to the renal capsule (T1–T2) demonstrate 5-year disease-free

survivals of 90–100%. Tumors extending beyond the renal capsule (T3 or T4) and node-positive tumors have 5-year disease-free survivals of 50–60% and 0–15%, respectively. One subgroup of patients with nonlocalized disease has reasonable long-term survival, namely, those with solitary resectable metastases. In this setting, radical nephrectomy with resection of the solitary metastasis results in 5-year disease-free survival rates of 15–30%.

► When to Refer

- Refer patients with solid renal masses or complex cysts to a urologist for further evaluation.
- Refer patients with renal cell carcinoma to a urologic surgeon for surgical excision.
- Refer patients with metastatic disease to an oncologist and urologist.

Lalani AA et al. Systemic treatment of metastatic clear cell renal cell carcinoma in 2018: current paradigms, use of immunotherapy, and future directions. *Eur Urol*. 2019;75:100. [PMID: 30327274]

Motzer RJ et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277. [PMID: 29562145]

Rini BI et al; KEYNOTE-426 Investigators. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1116. [PMID: 30779529]

Sanchez A et al. Current management of small renal masses, including patient selection, renal tumor biopsy, active surveillance, and thermal ablation. *J Clin Oncol*. 2018;36:3591. [PMID: 30372390]

OTHER PRIMARY TUMORS OF THE KIDNEY

Oncocytomas account for 3–5% of renal tumors, are usually benign, and are indistinguishable from renal cell carcinoma on preoperative imaging. These tumors are seen in other organs, including the adrenals, salivary glands, and thyroid and parathyroid glands.

Angiomyolipomas are rare benign tumors composed of fat, smooth muscle, and blood vessels. They are most commonly seen in patients with tuberous sclerosis (often multiple and bilateral) or in young to middle-aged women. CT scanning may identify the fat component, which is diagnostic for angiomyolipoma. Asymptomatic lesions less than 5 cm in diameter usually do not require intervention; large lesions can spontaneously bleed. Acute bleeding can be treated by angiographic embolization or, in rare cases, nephrectomy. Lesions over 5 cm are often prophylactically treated with angioembolization to reduce the risk of bleeding.

SECONDARY CANCERS OF THE KIDNEY

The kidney is not an infrequent site for metastatic disease. Of the solid tumors, lung cancer is the most common (20%), followed by breast (10%), stomach (10%), and the contralateral kidney (10%). Lymphoma, both Hodgkin and non-Hodgkin, may also involve the kidney, although it tends to appear as a diffusely infiltrative process resulting in renal enlargement rather than a discrete mass.

TESTICULAR CANCERS (Germ Cell Tumors)



ESSENTIALS OF DIAGNOSIS

- ▶ Most common neoplasm in men aged 20–35 years.
- ▶ Patient typically discovers a painless nodule.
- ▶ Orchiectomy necessary for diagnosis.

► General Considerations

Malignant tumors of the testis are rare, with approximately five to six cases per 100,000 males reported in the United States each year. Ninety to 95 percent of all primary testicular tumors are germ cell tumors and can be divided into two major categories: **nonseminomas**, including embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (less than 1%), and mixed cell types (40%); and **seminomas** (35%). The lifetime probability of developing testicular cancer is 0.3% for an American male.

Approximately 5% of testicular cancers develop in a patient with a history of cryptorchidism, with seminoma being the most common. However, 5–10% of these tumors occur in the contralateral, normally descended testis. The relative risk of development of malignancy is higher for the intra-abdominal testis (1:20) and lower for the inguinal testis (1:80). Placement of the cryptorchid testis into the scrotum (orchidopexy) does not alter its malignant potential but does facilitate routine examination and cancer detection.

Testicular cancer is slightly more common on the right than the left, paralleling the increased incidence of cryptorchidism on the right side. One to 2 percent of primary testicular cancers are bilateral and up to 50% of these men have a history of unilateral or bilateral cryptorchidism. Primary bilateral testicular cancers may occur synchronously or asynchronously but tend to be of the same histology. Seminoma is the most common histologic finding in bilateral primary testicular cancers, while malignant lymphoma is the most common bilateral testicular tumor overall.

► Clinical Findings

A. Symptoms and Signs

The most common symptom of testicular cancer is painless enlargement of the testis. Sensations of heaviness are not unusual. Patients are usually the first to recognize an abnormality, yet often delay in seeking medical attention ranges from 3 to 6 months. Acute testicular pain resulting from intratesticular hemorrhage occurs in approximately 10% of cases. Ten percent of patients are asymptomatic at presentation, and 10% manifest symptoms relating to metastatic disease such as back pain (retroperitoneal metastases), cough (pulmonary metastases), or lower extremity edema (vena cava obstruction).

A discrete mass or diffuse testicular enlargement is noted in most cases. Secondary hydroceles may be present in 5–10% of cases. In advanced disease, supraclavicular adenopathy may be present, and abdominal examination may reveal a mass. Gynecomastia is seen in 5% of germ cell tumors.

B. Laboratory Findings

Several serum markers are important in the diagnosis and monitoring of testicular carcinoma, including human chorionic gonadotropin (hCG), alpha-fetoprotein, and lactate dehydrogenase. Alpha-fetoprotein is never elevated with pure seminomas, and while hCG is occasionally elevated in seminomas, levels tend to be lower than those seen with nonseminomas. Lactate dehydrogenase may be elevated with either type of tumor and is a marker for disease burden. Liver tests may be elevated in the presence of hepatic metastases, and anemia may be present in advanced disease.

C. Imaging

Scrotal ultrasound can readily determine whether a mass is intratesticular or extratesticular. Once the diagnosis of testicular cancer has been established by inguinal orchietomy, clinical staging of the disease is accomplished by chest, abdominal, and pelvic CT scanning.

► Staging

Testicular cancer is staged using the TNM system created based on extent of cancer in the testis, status of regional lymph nodes, the presence of metastases in distant lymph nodes or other viscera, and serum levels of tumor markers. Based on these features, germ cell tumors can be grouped to assign an overall stage: stage I lesion is confined to the testis; stage II demonstrates regional lymph node involvement in the retroperitoneum; and stage III indicates distant metastasis.

► Differential Diagnosis

An incorrect diagnosis is made at the initial examination in up to 25% of patients with testicular tumors. Scrotal ultrasonography should be performed if any uncertainty exists with respect to the diagnosis. Although most intratesticular masses are malignant, a benign lesion—epidermoid cyst—may rarely be seen. Epidermoid cysts are usually very small benign nodules located just underneath the tunica albuginea; occasionally, however, they can be large. Testicular lymphoma is discussed below.

► Treatment

Inguinal exploration with early vascular control of the spermatic cord structures is the initial intervention. If cancer cannot be excluded by examination of the testis, radical orchietomy is warranted. Scrotal approaches and open testicular biopsies should be avoided. Further therapy depends on the histology of the tumor as well as the clinical stage.

Patients with clinical stage I **seminomas** are candidates for surveillance (preferred), single-agent carboplatin, or adjuvant radiotherapy. Stage IIa and IIb seminomas (retroperitoneal disease less than 2 cm diameter in IIa and 2–5 cm in IIb) are treated by radical orchietomy plus retroperitoneal irradiation or primary systemic chemotherapy (etoposide and cisplatin or cisplatin, etoposide, and bleomycin) (Table 39–2). Seminomas of stage IIc (greater than 5-cm-diameter retroperitoneal nodes) and stage III receive

primary systemic chemotherapy. After chemotherapy, surgical resection of residual retroperitoneal nodes is warranted if the node is greater than 3 cm in diameter and positive on PET scan, since 40% will harbor residual carcinoma.

Up to 75% of clinical stage I **nonseminomas** are cured by orchietomy alone. Selected patients without specific risk factors have low-risk of recurrence and are generally offered surveillance after orchietomy. These criteria include (1) cancer is confined within the tunica albuginea; (2) cancer does not demonstrate vascular invasion; (3) tumor markers normalize after orchietomy; (4) radiographic imaging of the chest and abdomen shows no evidence of disease; and (5) the patient is reliable. Patients most likely to experience relapse on a surveillance regimen include those with predominantly embryonal cancer and those with vascular or lymphatic invasion identified in the orchietomy specimen. Alternatives to surveillance for clinical stage I nonseminomas include adjuvant chemotherapy (bleomycin, etoposide, cisplatin) (see Table 39–2) or retroperitoneal lymph node dissection.

Following orchietomy, patients with bulky retroperitoneal disease (greater than 5-cm nodes) or metastatic nonseminomas are treated with combination chemotherapy (cisplatin and etoposide or cisplatin, etoposide, and bleomycin) (Table 39–2). If tumor markers normalize and a residual mass greater than 1 cm persists on imaging studies, it is resected because 15–20% will harbor residual cancer and 40% will harbor teratomas. Even if patients have a complete response to chemotherapy, some clinicians advocate retroperitoneal lymphadenectomy since 10% of patients may harbor residual carcinoma and 10%, retroperitoneal teratoma. If tumor markers fail to normalize following primary chemotherapy, salvage chemotherapy is required (cisplatin, etoposide, and ifosfamide).

Postoperative active surveillance by the clinician and patient means patients are followed up every 2–6 months for the first 2 years and every 4–6 months in the third year. For nonseminomas, tumor markers are obtained at each visit, and chest radiographs and abdominal and pelvic CT scans are obtained every 4–6 months. For seminomas, serum tumor markers may be obtained (optional), chest imaging is obtained only as clinically indicated, and abdominal and pelvic CT scans are performed every 3–6 months. Follow-up continues beyond the initial 3 years; however, 80% of relapses will occur within the first 2 years. With rare exceptions, patients who relapse can be cured by chemotherapy or surgery.

► Prognosis

The 5-year disease-free survival rates for stage I and IIa **seminomas** (retroperitoneal disease less than 2 cm in diameter) treated by radical orchietomy and retroperitoneal irradiation are 98% and 92–94%, respectively. Ninety-five percent of patients with stage III disease attain a complete response following orchietomy and chemotherapy. The 5-year disease-free survival for patients with stage I **nonseminomas** (includes all treatments) ranges from 96% to 100%. For low-volume stage II disease, a 5-year disease-free survival of 90% is expected. Patients with

bulky retroperitoneal or disseminated disease treated with primary chemotherapy followed by surgery have a 5-year disease-free survival rate of 55–80%.

► When to Refer

Refer all patients with solid masses of the testis to a urologist and a medical oncologist if metastatic disease is suspected.

Goldberg H et al. Germ cell testicular tumors—contemporary diagnosis, staging and management of localized and advanced disease. *Urology*. 2019;125:8. [PMID: 30597167]

King J et al. Management of residual disease after chemotherapy in germ cell tumors. *Curr Opin Oncol*. 2020;32:250. [PMID: 32168037]

Pierorazio PM et al. Performance characteristics of clinical staging modalities for early stage testicular germ cell tumors: a systematic review. *J Urol*. 2020;203:894. [PMID: 31609176]

SECONDARY CANCERS OF THE TESTIS

Secondary cancers of the testis are rare. In men over the age of 50 years, lymphoma is the most common. Overall, it is the most common secondary neoplasm of the testis, accounting for 5% of all testicular cancers. It may be seen in three clinical settings: (1) late manifestation of widespread lymphoma, (2) the initial presentation of clinically occult disease, and (3) primary extranodal disease. Radical orchietomy is indicated to make the diagnosis. Prognosis is related to the stage of disease.

Metastasis to the testis is rare. The most common primary site of origin is the prostate, followed by the lung, gastrointestinal tract, melanoma, and kidney.

CANCER COMPLICATIONS & EMERGENCIES

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SPINAL CORD COMPRESSION



ESSENTIALS OF DIAGNOSIS

- Complication of metastatic solid tumor, lymphoma, or plasma cell myeloma.
- Back pain is most common presenting symptom.
- Prompt diagnosis is essential because once a severe neurologic deficit develops, it is often irreversible.
- Emergent treatment may prevent or potentially reverse paresis and urinary and bowel incontinence.

► General Considerations

Cancers that cause spinal cord compression most commonly metastasize to the vertebral bodies, resulting in physical damage to the spinal cord from edema, hemorrhage,

and pressure-induced ischemia to its vasculature. Persistent compression can result in irreversible changes to the myelin sheaths resulting in permanent neurologic impairment.

Prompt diagnosis and therapeutic intervention are essential, since the probability of reversing neurologic symptoms largely depends on the duration of symptoms. Patients who are treated promptly after symptoms appear may have partial or complete return of function and, depending on tumor sensitivity to specific treatment, may respond favorably to subsequent anticancer therapy.

► Clinical Findings

A. Symptoms and Signs

Back pain at the level of the tumor mass occurs in over 80% of cases and may be aggravated by lying down, weight bearing, sneezing, or coughing; it usually precedes the development of neurologic symptoms or signs. Since involvement is usually epidural, a mixture of nerve root and spinal cord symptoms often develops. Progressive weakness and sensory changes commonly occur. Bowel and bladder symptoms progressing to incontinence are late findings.

The initial findings of impending cord compression may be quite subtle, and there should be a high index of suspicion when back pain or weakness of the lower extremities develops in a cancer patient.

B. Imaging

MRI is usually the initial imaging procedure of choice in a cancer patient with new-onset back pain. If the back pain symptom is nonspecific, a whole-body PET-CT scan with ¹⁸F-2-deoxyglucose may be a useful screening procedure. Bone radiographs are neither sensitive nor specific for the evaluation of a cancer patient with back pain. When neurologic findings suggest spinal cord compression, an emergent MRI should be obtained; the MRI should survey the entire spine to define all areas of tumor involvement for treatment planning purposes. MRI has a sensitivity of 93% and a specificity of 97% for diagnosis of metastatic spinal cord compression.

► Treatment

Patients with a known cancer diagnosis found to have epidural impingement of the spinal cord should be given corticosteroids immediately. The initial dexamethasone dose is 10 mg intravenously followed by 4–6 mg every 6 hours intravenously or orally. Patients without a known diagnosis of cancer should have emergent surgery to relieve the impingement and obtain a pathologic specimen; preoperative corticosteroids should not be given since they might compromise the pathology results. Patients with solid tumors who have a single area of compression and who are considered candidates for surgery are best treated first with surgical decompression followed by radiation therapy. Better outcomes (ie, improved ability to ambulate and improved bladder and bowel function) occur in patients who undergo surgery followed by

radiation therapy than in those who receive radiation alone. If multiple vertebral body levels are involved with cancer, fractionated radiation therapy is the preferred treatment option. Corticosteroids are generally tapered toward the end of radiation therapy. A scoring system exists for patients presenting with spinal cord metastases to identify those with poor survival times who would be best managed with supportive care or single fraction palliative radiation.

Boussios S et al. Metastatic spinal cord compression: unraveling the diagnostic and therapeutic challenges. *Anticancer Res.* 2018;38:4987. [PMID: 30194142]

Hoskin PJ et al. Effect of single-fraction vs multifraction radiotherapy on ambulatory status among patients with spinal canal compression from metastatic cancer: the SCORAD randomized clinical trial. *JAMA.* 2019;322:2084. [PMID: 31794625]

Lawton AJ et al. Assessment and management of patients with metastatic spinal cord compression: a multidisciplinary review. *J Clin Oncol.* 2019;37:61. [PMID: 30395488]

MALIGNANT EFFUSIONS

ESSENTIALS OF DIAGNOSIS

- ▶ Occur in pleural, pericardial, and peritoneal spaces.
- ▶ Caused by direct neoplastic involvement of serous surface or obstruction of lymphatic drainage.
- ▶ Half of undiagnosed effusions in patients not known to have cancer are malignant.

► General Considerations

The development of an effusion in the pleural, pericardial, or peritoneal space may be the initial finding in a patient with cancer, or an effusion may appear during the course of disease progression. Direct involvement of the serous surface with tumor is the most frequent initiating cause of the accumulation of fluid. The most common malignancies causing pleural and pericardial effusions are lung and breast cancers; the most common malignancies associated with malignant ascites are ovarian, colorectal, stomach, and pancreatic cancers.

► Clinical Findings

A. Symptoms and Signs

Patients with pleural and pericardial effusions complain of shortness of breath and orthopnea. Patients with ascites complain of abdominal distention and discomfort. Cardiac tamponade causing pressure equalization in the chambers impairs both filling and cardiac output and can be life-threatening. Signs of tamponade include tachycardia, muffled heart sounds, pulsus paradoxus, and hypotension. Signs of pleural effusions include decreased breath sounds, egophony, and percussion dullness.

B. Laboratory Findings

Malignancy is confirmed as the cause of an effusion when analysis of the fluid specimen shows malignant cells in either the cytology or cell block specimen.

C. Imaging

The presence of effusions can be confirmed with radiographic studies or ultrasonography.

► Differential Diagnosis

The differential diagnosis of a malignant pleural or pericardial effusion includes nonmalignant processes, such as infection, pulmonary embolism, heart failure, and trauma. The differential diagnosis of malignant ascites includes similar benign processes, such as heart failure, cirrhosis, peritonitis, and pancreatic ascites. Bloody effusions are usually due to cancer, but a bloody pleural effusion can also be due to pulmonary embolism, trauma and, occasionally, infection. Chylous pleural or ascitic fluid is generally associated with obstruction of lymphatic drainage as might occur in lymphoma.

► Treatment

The development of a malignant effusion is a late-stage manifestation of the cancer. Treatment is tailored to the underlying cancer, whether with targeted therapy, chemotherapy, or immunotherapy, depending on tumor testing results. Effective systemic treatment can lead to regression of the effusion. Acute symptoms related to the effusion often require urgent intervention with drainage of the effusion. Decisions regarding palliative management of malignant effusion are in large part dictated by the patient's symptoms and goals of care.

A. Pleural Effusion

A pleural effusion that is symptomatic may be managed initially with a **large volume thoracentesis**. In some patients, the effusion slowly reaccumulates, which allows for periodic thoracentesis when the patient becomes symptomatic. However, in many patients, the effusion reaccumulates quickly, causing rapid return of shortness of breath. For those patients, two other management options exist: pleurodesis or indwelling pleural catheter (eg, PleurX). Chest tube drainage followed by pleurodesis involves placement of a chest tube that is connected to closed water seal drainage. After lung expansion is confirmed on a chest radiograph, a sclerosing agent (such as talc slurry or doxycycline) is injected into the catheter. Patients should be premedicated with analgesics. Pleurodesis will not be successful if the lung cannot be reexpanded. These patients are better managed with placement of an indwelling catheter that can be drained by a family member or a visiting nurse. This procedure is often preferable for patients with short life expectancies or for those who do not respond to pleurodesis. In a meta-analysis of randomized controlled trials comparing indwelling pleural catheter with pleurodesis, indwelling pleural catheters resulted

in shorter hospital stays and fewer repeat pleural interventions, but increased rates of cellulitis.

B. Pericardial Effusion

Fluid may be removed by a needle aspiration or by placement of a catheter for more thorough drainage. As with pleural effusions, most pericardial effusions will reaccumulate. Management options for recurrent, symptomatic effusions include prolonged catheter drainage (for several days until drainage has decreased to 20–30 mL/day) or surgical intervention such as a pericardiotomy or pericardectomy.

C. Malignant Ascites

Patients with malignant ascites not responsive to chemotherapy are generally treated with repeated large-volume paracenteses. Since the frequency of drainage to maintain comfort can compromise the patient's quality of life, other alternatives include placement of a catheter or port so that the patient, family member, or visiting nurse can drain fluid as needed at home. For patients with portal hypertension from large hepatic masses, diuretics (such as spironolactone 100 mg with furosemide 20–40 mg orally daily) may be useful to decrease the need for repeated paracentesis.

Asciak R et al. Malignant pleural effusion: from diagnostics to therapeutics. *Clin Chest Med*. 2018;39:181. [PMID: 29433714]

Feller-Kopman DJ et al. Management of malignant pleural effusions. An official ATS/STS/STR clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198:839. [PMID: 30272503]

Iyer NP et al. Indwelling pleural catheter versus pleurodesis for malignant pleural effusions. A systematic review and meta-analysis. *Ann Am Thorac Soc*. 2019;16:124. [PMID: 30272486]

Walker S et al. Malignant pleural effusion management: keeping the flood gates shut. *Lancet Respir Med*. 2020;8:609. [PMID: 31669226]

HYPERCALCEMIA



ESSENTIALS OF DIAGNOSIS

- Most common paraneoplastic endocrine syndrome.
- Usually symptomatic and severe ($\geq 15 \text{ mg/dL}$ [3.75 mmol/L]); accounts for most inpatients with hypercalcemia.
- The neoplasm is clinically apparent in nearly all cases when hypercalcemia is detected.

► General Considerations

Hypercalcemia affects 20–30% of cancer patients at some point during their illness. The most common cancers causing hypercalcemia are myeloma, breast carcinoma, and NSCLC. Hypercalcemia is caused by one of three mechanisms: systemic effects of tumor-released proteins, direct osteolysis of bone by tumor, or vitamin D-mediated osteoabsorption.

► Clinical Findings

A. Symptoms and Signs

Symptoms and signs of hypercalcemia can be subtle; more severe symptoms occur with higher levels of hypercalcemia and with a rapidly rising calcium level. Early symptoms typically include anorexia, nausea, fatigue, constipation, and polyuria; later findings may include muscular weakness and hyporeflexia, confusion, psychosis, tremor, and lethargy.

B. Laboratory Findings

Symptoms and signs are caused by free calcium; as calcium is bound by protein in the serum, the measured serum calcium will underestimate the free or ionized calcium in patients with low albumin levels. Free ionized calcium can be measured. When the corrected serum calcium rises above 12 mg/dL (3 mmol/L), especially if the rise occurs rapidly, sudden death due to cardiac arrhythmia or asystole may occur. Initial work-up for hypercalcemia includes obtaining serum PTH, PTHrP, and calcitonin levels. The presence of hypercalcemia does not invariably indicate a dismal prognosis, especially in patients with breast cancer, myeloma, or lymphoma.

C. ECG

Electrocardiography in hypercalcemia often shows a shortening of the QT interval.

► Treatment

Emergency management should begin with the initiation of intravenous fluids with 0.9% saline at 100–300 mL/h to ensure rehydration with brisk urinary output of the often volume-depleted patient. If kidney function is normal or only marginally impaired, a bisphosphonate should be given. Choices include pamidronate, 60–90 mg intravenously over 2–4 hours, or zoledronic acid, 4 mg intravenously over 15 minutes. Zoledronic acid is more potent than pamidronate and has the advantage of a shorter administration time as well as a longer duration of effect. Once hypercalcemia is controlled, treatment directed at the cancer should be initiated if possible. In the event that the hypercalcemia becomes refractory to repeated doses of bisphosphonates, other agents that can help control hypercalcemia (at least temporarily) include calcitonin and denosumab; corticosteroids can be useful in patients with myeloma and lymphoma. Salmon calcitonin, 4–8 international units/kg given subcutaneously or intramuscularly every 12 hours, can be used in patients with severe, symptomatic hypercalcemia; its onset of action is within hours but its hypocalcemic effect wanes in 2–3 days. Denosumab, 120 mg given subcutaneously weekly for 4 weeks followed by monthly administration, is a choice for long-term management of bisphosphonate-refractory hypercalcemia or for patients with kidney dysfunction that precludes use of a bisphosphonate.

Zagzag J et al. Hypercalcemia and cancer: differential diagnosis and treatment. CA Cancer J Clin. 2018;68:377. [PMID: 30240520]

HYPERURICEMIA & TUMOR LYSIS SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Complication of treatment-associated tumor lysis of hematologic and rapidly proliferating malignancies.
- ▶ May be worsened by thiazide diuretics.
- ▶ Rapid increase in serum uric acid can cause acute urate nephropathy from uric acid crystallization.
- ▶ Reducing pre-chemotherapy serum uric acid is fundamental to preventing urate nephropathy.

► General Considerations

Tumor lysis syndrome (TLS) is seen most commonly following treatment of hematologic malignancies, such as acute lymphoblastic leukemia and Burkitt lymphoma. However, TLS can develop from any tumor highly sensitive to chemotherapy. TLS is caused by the massive release of cellular material including nucleic acids, proteins, phosphorus, and potassium. If both the metabolism and excretion of these breakdown products are impaired, hyperuricemia, hyperphosphatemia, and hyperkalemia will develop abruptly. Acute kidney injury may then develop from the crystallization and deposition of uric acid and calcium phosphate within the renal tubules, further exacerbating the hyperphosphatemia and hyperkalemia.

► Clinical Findings

A. Symptoms and Signs

Symptoms of hyperphosphatemia include nausea, vomiting, anorexia, muscle cramps, tetany, and seizures. High levels of phosphorus and co-precipitation with calcium can cause renal tubule blockage, further exacerbating the kidney injury. Hyperkalemia, due to release of intracellular potassium and impaired kidney excretion, can cause arrhythmias and sudden death.

B. Laboratory Findings

The laboratory diagnosis of TLS include at least two of the following criteria observed within a 24-hour period: uric acid 8 mg/dL or higher (476 μmol/L or higher), phosphate 4.5 mg/dL or higher (1.45 mmol/L or higher), potassium 6.0 mEq/L or more (6 mmol/L or more) (or a 25% increase from baseline for these parameters), and corrected serum calcium 7 mg/dL or lower (1.75 mmol/L or lower). A clinical diagnosis of TLS includes meeting the laboratory criteria and at least one clinical criterion: acute kidney injury (creatinine greater than or equal to $1.5 \times$ upper limit of normal or increase greater than 0.3 g/dL or urinary

output greater than 0.5 mL/kg/h for 6 hours) or cardiac arrhythmia, sudden cardiac death, or seizure.

► Treatment

Prevention is the most important factor in the management of TLS. Aggressive hydration at least 24 hours prior to chemotherapy as well as 24–48 hours after chemotherapy completion helps keep urine flowing and facilitates excretion of uric acid and phosphorus. It is recommended to maintain a urinary output of at least 100 mL/h, and a daily urine volume of at least 3 L/day. If evidence of volume overload or inadequate urinary output develops, loop diuretics can be used. Thiazide diuretics are contraindicated because they increase uric acid levels and can interact with allopurinol. For patients at moderate risk of developing TLS, eg, those with intermediate-grade lymphomas and acute leukemias, allopurinol should be given before starting chemotherapy with dose reductions for impaired kidney function. Rasburicase is given intravenously to patients at high risk for developing TLS, eg, those with high-grade lymphomas or acute leukemias with markedly elevated white blood cell counts. Rasburicase may also be considered for patients with baseline elevated uric acid who are being treated with venetoclax (Bcl-2 inhibitor) for chronic lymphocytic leukemia or in any patient in whom uric acid levels reach levels greater than 8 mg/dL despite treatment with allopurinol. Rasburicase cannot be given to patients with known glucose 6-phosphate dehydrogenase (G6PD) deficiency nor can it be given to pregnant or lactating women.

► When to Refer

Should urinary output drop, serum creatinine or potassium levels rise, or hyperphosphatemia persist, a nephrologist should be immediately consulted to evaluate the need for dialysis.

Durani U et al. Emergencies in haematology: tumor lysis syndrome. *Br J Haematol.* 2020;188:494. [PMID: 31774551]
Matuszkievicz-Rowinska J et al. Prevention and treatment of tumor lysis syndrome in the era of onco-nephrology progress. *Kidney Blood Press Res.* 2020;45:645. [PMID: 32998135]

INFECTIONS

Chapters 30 and 31 provide more detailed discussions of infections in the immunocompromised patient.

- 
- ### ESSENTIALS OF DIAGNOSIS
- ▶ In patients with neutropenia, infection is a medical emergency.
 - ▶ Although sometimes attributable to other causes, the presence of fever, defined as a single temperature $> 38.3^{\circ}\text{C}$ (101°F) or a temperature of $> 38^{\circ}\text{C}$ (100.4°F) for > 1 hour, must be assumed to be due to an infection.

► General Considerations

Many patients with disseminated neoplasms have increased susceptibility to infection. In some patients, this results from impaired defense mechanisms (eg, acute leukemia, Hodgkin lymphoma, plasma cell myeloma, chronic lymphocytic leukemia); in others, it results from the myelosuppressive and immunosuppressive effects of cancer chemotherapy or a combination of these factors. Complicating impaired defense mechanisms are the frequent presence of indwelling catheters, impaired mucosal surfaces, and colonization with more virulent hospital-acquired pathogens.

The source of a neutropenic febrile episode is determined in about 30% of cases through blood, urine, or sputum cultures. The bacterial organisms accounting for the majority of infections in cancer patients include gram-positive bacteria (coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Corynebacterium*, and streptococci) and gram-negative bacteria (*Escherichia coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*). Gram-positive organism infections are more common, but gram-negative infections are more serious and life-threatening. The risk of bacterial infections rises when the neutrophil count is below 500/mcL ($0.5 \times 10^9/\text{L}$); the risk markedly increases when the count falls below 100/mcL ($0.1 \times 10^9/\text{L}$) or when there is a prolonged duration of neutropenia, typically greater than 7 days.

► Clinical Findings

A thorough physical examination should be performed. Appropriate cultures (eg, blood, sputum, urine and, if indicated, cerebrospinal fluid) should always be obtained. Two sets of blood cultures should be drawn before starting antibiotics; if the patient has an indwelling catheter, one of the cultures should be drawn from the line. A chest radiograph should also be obtained.

► Treatment

Empiric antibiotic therapy needs to be initiated within 1 hour of presentation and following the collection of blood cultures in the febrile neutropenic patient. The choice of antibiotics depends on a number of different factors including the patient's clinical status and any localizing source of infection. If the patient is clinically well, monotherapy with an intravenous beta-lactam with anti-*Pseudomonas* activity (cefepime, ceftazidime, imipenem/cilastatin, piperacillin/tazobactam) should be started (see Infections in the Immunocompromised Patient, Chapter 30). If the patient is clinically ill with hypotension or hypoxia, an intravenous aminoglycoside or fluoroquinolone should be added for "double" gram-negative bacteria coverage. If there is a strong suspicion of a gram-positive organism, such as from a *S aureus* catheter infection, intravenous vancomycin can be given empirically. Low-risk patients may be treated with oral antibiotics in the outpatient setting.

Antibiotics should be continued until the neutrophil count is rising and greater than 500/mcL ($0.5 \times 10^9/\text{L}$) for at least 1 day and the patient has been afebrile for 2 days. If an organism is identified through the cultures, the

antibiotics should be adjusted to the antibiotic sensitivities of the isolate; treatment should be continued for the appropriate period of time and at least until the neutrophil count recovers and fever resolves.

For the neutropenic patient who is persistently febrile despite broad-spectrum antibiotics, an empiric antifungal drug should be added (amphotericin B, caspofungin, itraconazole, voriconazole, or liposomal amphotericin B).

Braga CC et al. Clinical implications of febrile neutropenia guidelines in the cancer patient population. *J Clin Oncol*. 2019;15:25. [PMID: 30629901]

Taplitz A et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *J Clin Oncol*. 2018;36:1443. [PMID: 29461916]

administered and monitored by a medical oncologist or hematologist. Selection of specific drugs or protocols for various types of cancer is usually based on results of clinical trials. Increasingly, newer agents are being identified that target specific molecular pathways. Yet both initial and acquired drug resistance remains a challenge. Described mechanisms of drug resistance include impaired membrane transport of drugs, enhanced drug metabolism, mutated target proteins, and blockage of apoptosis due to mutations in cellular proteins (see Table 39–2 for suggested agents for various cancers).

TOXICITY & DOSE MODIFICATION OF CHEMOTHERAPEUTIC AGENTS

Use of chemotherapy to treat cancer is generally guided by results from clinical trials in individual tumor types. The complexity of treating cancer has increased over the last decade as more drugs, including those with targeted mechanisms of action, have been approved by the US Food and Drug Administration (FDA) and introduced into general practice. Drug side effects and toxicities must be anticipated and carefully monitored. The short- and long-term toxicities of individual drugs are listed in Tables 39–3 and 39–12. Decisions on dose modifications for toxicities should be guided by the intent of therapy. In the palliative setting where the aim of therapy is to improve symptoms and quality of life, lowering doses to minimize toxicity is commonly done. However, when the goal of treatment is cure, dosing frequency and intensity should be maintained whenever possible.

PRIMARY CANCER TREATMENT

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SYSTEMIC CANCER THERAPY

Detailed guidelines from the NCCN for cancer treatment can be found at www.nccn.org.

Use of cytotoxic drugs, hormones, antiestrogens, and biologic agents has become a highly specialized and increasingly effective means of treating cancer, with therapy

Table 39–12. Commonly used supportive care agents.¹

Agent	Indication	Usual Dose	Adverse Effects
Allopurinol (Xyloprim)	Prevent hyperuricemia from tumor lysis syndrome	600–800 mg/day orally	Acute: none Delayed: rash
Dexrazoxane (Zinecard)	Prevent cardiomyopathy secondary to doxorubicin; anthracycline-induced injection site extravasation	10 times the doxorubicin dose intravenously before doxorubicin; 1000 mg/m ² intravenously on days 1 and 2, then 500 mg/m ² intravenously on day 3	Acute: nausea Delayed: myelosuppression, elevated transaminases
Leucovorin	Rescue after high-dose methotrexate; in combination with 5-fluorouracil for colon cancer	10 mg/m ² intravenously or orally every 6 hours; 20 mg/m ² or 200–500 mg/m ² intravenously before 5-fluorouracil; various doses	Acute: nausea, vomiting, diarrhea Delayed: stomatitis, fatigue
Mesna (Mesnex)	Prevent ifosfamide-induced hemorrhagic cystitis	20% of ifosfamide dose intravenously at 0, 4, and 8 hours; various doses	Acute: nausea, vomiting Delayed: fatigue
Palifermin (Kepivance)	Prevent mucositis following chemotherapy	60 mcg/kg/day intravenously for 3 days before and 3 days after chemotherapy	Acute: none Delayed: rash, fever, elevated serum amylase, erythema, edema
Radium (Ra)-223 dichloride (Xofigo)	Symptomatic bone metastases	50 kilobecquerel/kg (1.35 microCurie/kg) intravenously every 4 weeks for 6 cycles	Acute: nausea, vomiting, diarrhea, peripheral edema Delayed: myelosuppression
Rasburicase (Elitek)	Prevent hyperuricemia from tumor lysis syndrome	3–6 mg intravenously once	Acute: hypersensitivity, nausea, vomiting, diarrhea, fever, headache Delayed: rash, peripheral edema

(continued)

Table 39–12. Commonly used supportive care agents.¹ (continued)

Agent	Indication	Usual Dose	Adverse Effects
Bone-Modifying Agents			
Denosumab (Xgeva)	Osteolytic bone metastasis	120 mg subcutaneously every 4 weeks	Acute: nausea Delayed: hypocalcemia, hypophosphatemia, fatigue, osteonecrosis of the jaw
Pamidronate (Aredia)	Osteolytic bone metastasis, hypercalcemia of malignancy	90 mg intravenously every 3–4 weeks; 60–90 mg intravenously, may repeat after 7 days	Acute: nausea Delayed: dyspnea, arthralgia, bone pain, osteonecrosis of the jaw, nephrotoxicity, hypocalcemia
Zoledronic acid (Zometa)	Osteolytic bone metastasis, hypercalcemia of malignancy	4 mg intravenously every 3–4 weeks; 4 mg intravenously once, may repeat after 7 days	—
Growth Factors			
Darbepoetin alfa (Aranesp)	Chemotherapy-induced anemia	2.25 mcg/kg subcutaneously weekly; 500 mcg subcutaneously every 3 weeks	—
Epoetin alfa (Epogen, Procrit)	Chemotherapy-induced anemia	40,000 units subcutaneously once weekly; 150 units/kg subcutaneously three times a week	Acute: injection site reaction Delayed: hypertension, thromboembolic events, increased risk of tumor progression or recurrence
Filgrastim (Neupogen)	Febrile neutropenia prophylaxis, mobilization of peripheral stem cells	5–10 mcg/kg/day subcutaneously or intravenously once daily, treat past nadir	Acute: injection site reaction Delayed: bone pain
Pegfilgrastim (Neulasta)	Febrile neutropenia prophylaxis	6 mg subcutaneously once per chemotherapy cycle	—
Sargramostim (Leukine)	Myeloid reconstitution following bone marrow transplant, mobilization of peripheral blood stem cells	250 mcg/m ² intravenously daily until the absolute neutrophil count is > 1500 cells/mcL ($1.5 \times 10^9/L$) for 3 consecutive days	Acute: fever, rash, pruritus, nausea, vomiting, diarrhea, injection site reaction, dyspnea Delayed: asthenia, bone pain, mucositis, edema, arrhythmia

¹For amifostine, levoleucovorin, pilocarpine, samarium, strontium, filgrastim-sndz, and tbo-filgrastim, see Table 39–12 in *CMDT Online* at www.accessmedicine.com.

A CBC including a differential count, with absolute neutrophil count and platelet count, and liver and kidney tests should be obtained before the initiation of chemotherapy. In patients with good performance status, normal CBCs, as well as normal liver and kidney function, drugs are started at their full dose. When the intent of chemotherapy is cure, including treatment in the adjuvant setting, every attempt should be made to schedule chemotherapy on time and at full dose. A CBC with differential may be checked at mid cycle (to determine the nadir of the absolute neutrophil and platelet counts), and liver and kidney function tests should be obtained immediately before the next cycle of chemotherapy.

Dose reductions may be necessary for patients with impaired kidney or liver function depending on the clearance mechanism of the drug. For patients receiving chemotherapy for palliation, bone marrow toxicity can be managed with dose reductions or delaying the next treatment cycle. A schema for dose modification is shown in Table 39–13.

1. Bone Marrow Toxicity

A. Neutropenia

Granulocyte colony-stimulating factor (G-CSF), given as either daily subcutaneous injections (eg, filgrastim, 300 mcg

Table 39–13. A common scheme for dose modification of cancer chemotherapeutic agents.

Granulocyte Count	Platelet Count	Suggested Drug Dosage (% of Full Dose)
> 2000 cells/mcL ($2 \times 10^9/L$)	> 100,000/mcL ($100 \times 10^9/L$)	100%
1000–2000 cells/mcL ($1–2 \times 10^9/L$)	75,000–100,000/mcL ($75–100 \times 10^9/L$)	50%
< 1000 cells/mcL ($1 \times 10^9/L$)	< 50,000/mcL ($50 \times 10^9/L$)	0%

or 480 mcg) or as a one-time dose (pegfilgrastim, 6 mg) beginning 24 hours after cytotoxic chemotherapy is completed, reduces the duration and severity of granulocytopenia following cytotoxic chemotherapy (Table 39–12). The American Society of Clinical Oncology and NCCN guidelines recommend primary prophylaxis with G-CSF when there is at least a 20% risk of febrile neutropenia or when age, medical history, and disease characteristics put the patient at high risk for complications related to myelosuppression.

B. Anemia

Erythropoiesis-stimulating agents (ESAs) ameliorate the anemia and its associated symptoms caused by cancer chemotherapy but these drugs have untoward effects, including an increased risk of thromboembolism, and possibly a decreased survival due to cancer-related deaths as well as a shortened time to tumor progression. The FDA recommends that these drugs should not be used when the intent of chemotherapy is curative. Administration of red blood cell transfusions is an alternative for managing symptomatic anemia in chemotherapy patients.

ESAs can be an option in cancer patients with symptomatic anemia undergoing palliative treatment; patient preference is important in determining when to use ESAs or transfusions. When using ESAs, treatment should not be initiated until the hemoglobin is less than 10 g/dL (100 g/L) and the ESA held when the hemoglobin is greater than 12 g/dL (120 g/L). Epoetin alfa can be given subcutaneously at a dose of 40,000 units weekly or 150 units/kg three times weekly with a target hemoglobin of 11–12 g/dL (110–120 g/L). Darbepoetin alfa is given subcutaneously at a dose of 300–500 mcg every 3 weeks or 2.25 mcg weekly with the same target hemoglobin (see Table 39–12). To have maximum therapeutic effect, patients need to be iron replete. Uncontrolled hypertension is a contraindication to the use of ESAs; blood pressure must be controlled prior to initiation of this therapy.

C. Thrombocytopenia

Drug management of chemotherapy-induced thrombocytopenia is more limited. Two drugs that activate the thrombopoietin receptor, romiplostim and eltrombopag, are FDA approved for use in idiopathic thrombocytopenia, thrombocytopenia related to interferon therapy of hepatitis C, and thrombocytopenia in aplastic anemia. While these agents have been used in selected cases of refractory chemotherapy-related thrombocytopenia with some reports of success, trials to date have not demonstrated convincing efficacy in patients with chemotherapy-induced thrombocytopenia and neither agent is FDA approved for this indication.

2. Chemotherapy-Induced Nausea & Vomiting

A number of cytotoxic anticancer drugs can induce nausea and vomiting, which can be the most anticipated and stressful side effects for patients. Chemotherapy-induced nausea and vomiting is mediated in part by the stimulation of at least two central nervous system receptors, 5-hydroxytryptamine subtype 3 ($5HT_3$) and neurokinin subtype 1 (NK_1). Chemotherapy-induced nausea and vomiting can be

anticipatory, occurring even before chemotherapy administration; acute, occurring within minutes to hours of chemotherapy administration; or delayed, lasting up to 7 days. Chemotherapy drugs are classified into high, moderate, low, and minimal likelihoods of causing emesis (90%, 30–90%, 10–30%, less than 10%, respectively). Highly emetogenic chemotherapy drugs include carmustine, cisplatin, cyclophosphamide (at doses over 1.5 g/m²), dacarbazine, and streptozocin, or a combination of regularly dosed anthracyclines and cyclophosphamide. Moderately emetogenic chemotherapy drugs include azacitidine, bendamustine, carboplatin, crizotinib, cyclophosphamide, cytarabine, doxorubicin, epirubicin, ifosfamide, irinotecan, oxaliplatin, and temozolomide. Low emetogenic drugs include bortezomib, capecitabine, dabrafenib, dasatinib, docetaxel, erlotinib, etoposide, 5-fluorouracil, gemcitabine, hydroxyurea, lenalidomide, methotrexate, mitomycin, paclitaxel, pemetrexed, pomalidomide, and topotecan. Drugs with minimal risk of emesis include bevacizumab, bleomycin, cetuximab, decitabine, panitumumab, rituximab, trastuzumab, and vincristine.

Major advances have occurred in the development of highly effective antiemetic drugs. **Antagonists to the $5HT_3$ -receptor** include alosetron, dolasetron, granisetron, ondansetron, and palonosetron, as well as ramosetron and tropisetron (neither yet available in the United States). Ondansetron can be given either intravenously (8 mg or 0.15 mg/kg) or orally (24 mg once before highly emetogenic chemotherapy, 8 mg twice daily for moderately emetogenic chemotherapy). Doses of 8 mg can be repeated parenterally or orally every 8 hours. Dosing of granisetron is 1 mg or 0.01 mg/kg intravenously or 1–2 mg orally. Dolasetron is given once as an oral 100-mg dose. Palonosetron, a long-acting $5HT_3$ -receptor antagonist with high affinity for the receptor, is given once at a dose of 0.25 mg intravenously, both for acute and delayed emesis. As a class of drugs, the $5HT_3$ -receptor antagonists have the potential to cause electrocardiogram changes, including QT prolongation.

Antagonists to the NK_1 -receptor are aprepitant, fosaprepitant, and netupitant. Aprepitant is given as a 125-mg oral dose followed by an 80-mg dose on the second and third day along with a $5HT_3$ -receptor antagonist and dexamethasone to increase its immediate and delayed protective effect for highly emetogenic chemotherapy. Fosaprepitant, the intravenous formulation of the prodrug to aprepitant, can be given at a dose of 115 mg if followed by 2 days of aprepitant or at a dose of 150 mg if given alone. NEPA is a single-dose capsule consisting of a combination of netupitant and palonosetron.

For highly emetogenic chemotherapy (eg, cisplatin), patients should be offered a four-drug regimen (a $5HT_3$ -antagonist, dexamethasone, NK_1 -receptor antagonist, and olanzapine), all given on the first day (and if used, aprepitant given again on the second and third days with dexamethasone and olanzapine continued on days 2–4. For moderately emetogenic chemotherapy, standard regimens include both three-drug regimens (an NK_1 -antagonist, a $5HT_3$ -antagonist, and dexamethasone) or a two-drug combination ($5HT_3$ -antagonist and dexamethasone). Palonosetron is the preferred $5HT_3$ -blocker due to its greater

affinity for the 5HT₃-receptor and its longer half-life. For low emetogenic chemotherapy drugs, a single agent such as a 5HT₃-antagonist or prochlorperazine or dexamethasone can be given. A 25-mg suppository form of prochlorperazine may be used for patients unable to swallow oral medications. Another medication that is helpful for anticipatory or refractory nausea and vomiting is olanzapine, 10 mg given orally once.

The importance of treating chemotherapy-induced nausea and vomiting expectantly and aggressively beginning with the first course of chemotherapy cannot be overemphasized. Patients being treated in the clinic setting should always be given antiemetics for home use with written instructions as well as contact numbers to call for advice.

3. Gastrointestinal Toxicity

Untoward effects of cancer chemotherapy include damage to the more rapidly growing cells of the body such as the mucosal lining from the mouth through the gastrointestinal tract. Oral symptoms range from mild mouth soreness to frank ulcerations. Not uncommonly, mouth ulcerations will have superimposed candida or herpes simplex infections. In addition to receiving cytotoxic chemotherapy, a significant risk factor for development of oral mucositis is poor oral hygiene and existing caries or periodontal disease. Toxicity in the gastrointestinal tract usually manifests as diarrhea. Gastrointestinal symptoms can range from mild symptoms of loose stools to life-threatening diarrhea leading to dehydration and electrolyte imbalances. Drugs most commonly associated with causing mucositis in the mouth and the gastrointestinal tract are cytarabine, 5-fluorouracil, and methotrexate.

Patients undergoing treatment for head and neck cancer with concurrent chemotherapy and radiation therapy have a very high risk of developing severe mucositis.

Preventive strategies for oral mucositis include pretreatment dental care, particularly for all head and neck cancer patients and any cancer patient with poor dental hygiene who will be receiving chemotherapy. For patients receiving 5-fluorouracil, simple measures such as ice chips in the mouth for 30 minutes during infusion can reduce the incidence and severity of mucositis. Once mucositis is encountered, superimposed fungal infections should be treated with topical antifungal medications (oral nystatin mouth suspensions, or clotrimazole troches) or systemic therapy (fluconazole 100–400 mg orally daily). Suspected herpetic infections can be treated with acyclovir (up to 800 mg orally five times daily) or valacyclovir (1 g orally twice daily). Mucositis may also be managed with mouthwashes; it is also important to provide adequate pain medication.

Another strategy for prevention of oral mucositis is the use of palifermin, the recombinant keratinocyte growth factor inhibitor. Prophylaxis with intravenous palifermin (60 mcg/kg/day) for patients receiving high-dose chemotherapy can reduce the incidence and duration of mucositis (Table 39–12).

Diarrhea is most associated with 5-fluorouracil, capecitabine, and irinotecan as well as the tyrosine kinase inhibitors (dasatinib, imatinib, nilotinib, regorafenib, sorafenib, sunitinib) and epithelial growth factor inhibitors

(cetuximab, erlotinib, panitumumab). Mild to moderate diarrhea can be managed with oral antidiarrheal medication (loperamide, 4 mg initially followed by 2 mg every 2–4 hours until bowel movements are formed). Occasionally, severe diarrhea will cause dehydration, electrolyte imbalances, and acute kidney injury; these patients require inpatient management with aggressive intravenous hydration and electrolyte replacement. Octreotide, 100–150 mcg subcutaneously three times daily, can be useful.

4. Skin Toxicity

Dermatologic complications from cancer chemotherapy can include hyperpigmentation (busulfan, hydroxyurea, liposomal doxorubicin), alopecia, photosensitivity, nail changes, acral erythema, and generalized rashes. Acral erythema (hand-foot syndrome), most commonly associated with administration of capecitabine, 5-fluorouracil, and liposomal doxorubicin, manifests as painful palms or soles accompanied by erythema, progressing to blistering, desquamation, and ulceration in its worst forms. Strategies for prevention of acral erythema include oral pyridoxine, 200 mg daily, and applying cold packs to the extremities during chemotherapy administration. Agents targeting the epidermal growth factor pathway can cause an acne-like rash; the development of the rash may identify those who will respond to the drug. Inhibitors of the tyrosine kinase pathway are also associated with a high incidence of dermatologic complications, such as rash and acral erythema.

5. Miscellaneous Drug-Specific Toxicities

The toxicities of individual drugs are summarized in Tables 39–3 and 39–12; however, several of these toxicities warrant additional mention, since they occur with frequently administered agents, and special measures are often indicated.

A. Hemorrhagic Cystitis Induced by Cyclophosphamide or Ifosfamide

Patients receiving cyclophosphamide must maintain a high fluid intake prior to and following the administration of the drug and be counseled to empty their bladders frequently. Early symptoms suggesting bladder toxicity include dysuria and increased frequency of urination. Should microscopic hematuria develop, it is advisable to stop the drug temporarily or switch to a different alkylating agent, to increase fluid intake, and to administer a urinary analgesic such as phenazopyridine. The neutralizing agent, mesna, can be used for patients in whom cystitis develops. With severe cystitis, large segments of bladder mucosa may be shed, resulting in prolonged gross hematuria. Such patients should be observed for signs of urinary obstruction and may require cystoscopy for removal of obstructing blood clots. The cyclophosphamide analog ifosfamide can cause severe hemorrhagic cystitis when used alone. However, when its use is followed by a series of doses of the neutralizing agent mesna, bladder toxicity can be prevented (Table 39–12).

B. Neuropathy Due to Vinca Alkaloids and Other Chemotherapy Drugs

Neuropathy is caused by a number of different chemotherapy drugs, the most common being vincristine. The peripheral neuropathy can be sensory, motor, autonomic, or a combination of these types. In its mildest form, it consists of paresthesias of the fingers and toes. Occasionally, acute jaw or throat pain can develop as a form of trigeminal or glossopharyngeal neuralgia. With continued vincristine therapy, the paresthesias extend to the proximal interphalangeal joints, hyporeflexia appears in the lower extremities, and significant weakness can develop. Other drugs in the vinca alkaloid class as well as the taxane drugs (docetaxel and paclitaxel) and agents to treat myeloma (bortezomib and thalidomide) cause similar toxicity.

Constipation is the most common symptom of autonomic neuropathy associated with the vinca alkaloids. Patients receiving these drugs should be started on mild cathartics and other agents (Table 15–4); otherwise, severe impaction may result from an atonic bowel. More serious autonomic involvement can lead to acute intestinal obstruction with signs indistinguishable from those of an acute abdomen. Bladder neuropathies are uncommon but may be severe. These two complications are absolute contraindications to continued vincristine therapy.

C. Methotrexate Toxicity

Methotrexate, a folate antagonist, is a commonly used component of regimens to treat patients with leptomeningeal disease, acute lymphoblastic leukemia, and sarcomas. Methotrexate is almost entirely eliminated by the kidney. Methotrexate toxicity affects cells with rapid turnover, including the bone marrow and mucosa resulting in myelosuppression and mucositis. Methotrexate can also damage the liver and kidney manifesting as elevated serum liver enzymes and creatinine. High-dose methotrexate, usually defined as a dose of 500 mg/m^2 or more given over 4–36 hours, would be lethal without “rescue” of the normal tissues. Leucovorin, a form of folate, will reverse the toxic effects of methotrexate and is given until serum methotrexate levels are in the safe range (less than 0.05 mmol/L). It is crucial that high-dose methotrexate and leucovorin are given precisely according to protocol as deviations of the timing of methotrexate delivery or delay in rescue can result in death. In a patient with kidney disease or an effusion, prolonged rescue with leucovorin is necessary.

Vigorous hydration and bicarbonate loading can help prevent crystallization of high-dose methotrexate in the renal tubular epithelium and consequent nephrotoxicity. Daily monitoring of the serum creatinine is mandatory. If possible, drugs impairing methotrexate excretion, such as aspirin, nonsteroidal anti-inflammatory drugs, amiodarone, omeprazole, penicillin, phenytoin, and sulfas, should be stopped before methotrexate administration.

D. Cardiotoxicity from Anthracyclines and Other Chemotherapy Drugs

A number of cancer chemotherapy drugs are associated with cardiovascular complications including traditional

drugs such as anthracyclines as well as new targeted agents. The anthracycline drugs, including doxorubicin, daunomycin, epirubicin, and idarubicin, can produce acute (during administration), subacute (days to months following administration), and delayed (years following administration) cardiac toxicity. The most feared complication is the delayed development of heart failure. Risk factors for this debilitating toxicity include the anthracycline cumulative dose, age over 70, previous or concurrent irradiation of the chest, preexisting cardiac disease, and concurrent administration of chemotherapy drugs such as trastuzumab. The problem is greatest with doxorubicin because it is the most commonly administered anthracycline due to its major role in the treatment of lymphomas, sarcomas, breast cancer, and certain other solid tumors. Patients receiving anthracyclines should have an assessment of left ventricular ejection fraction (LVEF). If the LVEF is greater than 50%, anthracyclines can be administered; if the LVEF is less than 30%, these drugs should not be given. For patients with intermediate values, anthracyclines can be cautiously given, if necessary, at lower doses with LVEF monitoring between doses. In general, patients should not receive doses in excess of 450 mg/m^2 ; the dose should be lower if prior chest radiotherapy has been given. Unfortunately, toxicity may be irreversible and frequently fatal at total dosage levels above 550 mg/m^2 . At lower doses (eg, 350 mg/m^2), the symptoms and signs of cardiac failure generally respond well to medical therapy and discontinuation of the anthracycline. Doxorubicin and daunomycin have been formulated as liposomal products; these drugs, approved for use in patients with Kaposi sarcoma and sometimes in other cancers as a substitute for the conventional anthracyclines, appear to have less potential for cardiac toxicity.

As molecular mechanisms for cancer have been increasingly delineated, therapies have been developed that better target these mechanisms. Therapies targeting oncogenic pathways include (1) HER2 inhibitors (lapatinib, pertuzumab, trastuzumab, ado-trastuzumab emtansine); (2) VEGF signaling pathway inhibitors (afilbercept, axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, ramucirumab, regorafenib, sorafenib, sunitinib, vandetanib); (3) multitargeted tyrosine kinase inhibitors (dasatinib, nilotinib, ponatinib); (4) proteasome inhibitors (bortezomib, carfilzomib); and (5) immune checkpoint inhibitors (atezolizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab). Many of the pathways targeted by these drugs share a common biologic pathway in cardiac tissue. Untoward cardiac events are being increasingly reported with these agents, including arrhythmias, cardiac ischemia, myocarditis, thrombosis, and heart failure.

E. Cisplatin Nephrotoxicity and Neurotoxicity

Cisplatin is effective in treating testicular, bladder, head and neck, lung, and ovarian cancers. With cisplatin, the serious side effects of nephrotoxicity and neurotoxicity must be anticipated and aggressively managed. Patients must be vigorously hydrated prior to, during, and after cisplatin administration. Both kidney function and electrolytes must be monitored. Low serum magnesium, potassium, and sodium levels can develop. The neurotoxicity is usually

manifested as a peripheral neuropathy of mixed sensorimotor type and may be associated with painful paresthesias. Development of neuropathy typically occurs after cumulative doses of 300 mg/m². Ototoxicity is a potentially serious manifestation of neurotoxicity and can progress to deafness. The second-generation platinum analog, carboplatin, is non-nephrotoxic, although it is myelosuppressive. In the setting of preexisting kidney disease or neuropathy, carboplatin is occasionally substituted for cisplatin.

F. Bleomycin Toxicity

See online text at www.accessmedicine.com/cmdt.

PROGNOSIS

Patients receiving chemotherapy for curative intent will often tolerate side effects with the knowledge that the treatment may result in eradication of their cancer. Patients receiving therapy for palliative intent often have their therapy tailored to improve quality of life while minimizing

major side effects. A valuable sign of clinical improvement is the general well-being of the patient. Although general well-being is a combination of subjective factors (possibly partly a placebo effect) and objective factors, it nonetheless serves as a sign of clinical improvement along with improved appetite and weight gain and increased “performance status” (eg, ambulatory versus bedridden). Evaluation of factors such as activity status enables the clinician to judge whether the net effect of chemotherapy is worthwhile palliation (see Chapter 5).

Babiker HM et al. Cardiotoxic effects of chemotherapy: a review of both cytotoxic and molecular targeted oncology therapies and their effect on the cardiovascular system. *Crit Rev Oncol Hematol*. 2018;126:186. [PMID: 29759560]

Okada Y et al. One-day versus three-day dexamethasone in combination with palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a systematic review and individual patient data-based meta-analysis. *Oncologist*. 2019;24:1593. [PMID: 31217343]

40

Genetic & Genomic Disorders

Reed E. Pyeritz, MD, PhD

ACUTE INTERMITTENT PORPHYRIA



ESSENTIALS OF DIAGNOSIS

- ▶ Unexplained abdominal crisis, generally in young women.
- ▶ Acute peripheral or central nervous system dysfunction; recurrent psychiatric illnesses.
- ▶ Hyponatremia.
- ▶ Porphobilinogen in the urine during an attack.

abdomen as to lead to exploratory laparotomy. Because the origin of the abdominal pain is neurologic, there is an absence of fever and leukocytosis. Complete recovery between attacks is usual. Any part of the nervous system may be involved, with evidence for autonomic and peripheral neuropathy. Peripheral neuropathy may be symmetric or asymmetric and mild or profound; in the latter instance, it can even lead to quadriplegia with respiratory paralysis. Other central nervous system manifestations include seizures, altered consciousness, psychosis, and abnormalities of the basal ganglia. Hyponatremia may further cause or exacerbate central nervous system manifestations.

B. Laboratory Findings

Often there is profound hyponatremia. The diagnosis can be confirmed by demonstrating an increased amount of porphobilinogen in the urine during an acute attack. Freshly voided urine is of normal color but may turn dark upon standing in light and air.

Most families have different mutations in *HMBS* causing AIP. Mutations can be detected in 90% of patients and used for presymptomatic and prenatal diagnosis.

► Prevention

Avoidance of factors known to precipitate attacks of AIP—especially drugs—can reduce morbidity. Sulfonamides and barbiturates are the most common culprits; others are listed in Table 40–1 and on the Internet (www.drugs-porphyria.org). Starvation diets and prolonged fasting also cause attacks and so must be avoided. Hormonal changes during pregnancy can precipitate crises.

► Treatment

Treatment with a high-carbohydrate diet diminishes the number of attacks in some patients and is a reasonable empiric gesture considering its benignity. Acute attacks may be life-threatening and require prompt diagnosis, withdrawal of the inciting agent (if possible), and treatment with analgesics and intravenous glucose in saline and hematin. A minimum of 300 g of carbohydrate per day should be provided orally or intravenously. Electrolyte

► General Considerations

Though there are several different types of porphyrias, the one with the most serious consequences and the one that usually presents in adulthood is acute intermittent porphyria (AIP), which is inherited as an autosomal dominant condition, though it remains clinically silent in most patients who carry a mutation in *HMBS*. Clinical illness usually develops in women. Symptoms begin in the teens or 20s, but onset can begin after menopause in rare cases. The disorder is caused by partial deficiency of hydroxymethylbilane synthase activity, leading to increased excretion of aminolevulinic acid and porphobilinogen in the urine. The diagnosis may be elusive if not specifically considered. The characteristic abdominal pain may be due to abnormalities in autonomic innervation in the gut. In contrast to other forms of porphyria, cutaneous photosensitivity is absent in AIP. Attacks are precipitated by numerous factors, including drugs and intercurrent infections. Harmful and relatively safe drugs for use in treatment are listed in Table 40–1. Hyponatremia may be seen, due in part to inappropriate release of antidiuretic hormone, although gastrointestinal loss of sodium in some patients may be a contributing factor.

► Clinical Findings

A. Symptoms and Signs

Patients show intermittent abdominal pain of varying severity, and in some instances, it may so simulate an acute

Table 40-1. Some of the “unsafe” and “probably safe” drugs used in the treatment of acute porphyrias.

Unsafe	Probably Safe
Alcohol	Acetaminophen
Alkylating agents	Amitriptyline
Barbiturates	Aspirin
Carbamazepine	Atropine
Chloroquine	Beta-adrenergic blockers
Chlorpropamide	Chloral hydrate
Clonidine	Chlordiazepoxide
Dapsone	Corticosteroids
Ergots	Diazepam
Erythromycin	Digoxin
Estrogens, synthetic	Diphenhydramine
Food additives	Guanethidine
Glutethimide	Hyoscine
Griseofulvin	Ibuprofen
Hydralazine	Imipramine
Ketamine	Insulin
Meprobamate	Lithium
Methyldopa	Naproxen
Metoclopramide	Nitrofurantoin
Nortriptyline	Opioid analgesics
Pentazocine	Penicillamine
Phenytoin	Penicillin and derivatives
Progestins	Phenothiazines
Pyrazinamide	Procaine
Rifampin	Streptomycin
Spironolactone	Succinylcholine
Succinimides	Tetracycline
Sulfonamides	Thiouracil
Theophylline	
Tolazamide	
Tolbutamide	
Valproic acid	

balance requires close attention. Hematin therapy should be undertaken with full recognition of adverse consequences, especially phlebitis and coagulopathy. The intravenous dosage is up to 4 mg/kg once or twice daily. Liver transplantation may provide an option for patients with disease poorly controlled by medical therapy.

► When to Refer

- For management of severe abdominal pain, seizures, or psychosis.
- For preventive management when a patient with porphyria contemplates pregnancy.
- For genetic counseling and molecular diagnosis.

► When to Admit

The patient should be hospitalized for an acute attack when accompanied by mental status changes, seizure, or hyponatremia.

Bissell DM et al. Porphyria. *N Engl J Med.* 2017;377:862. [PMID: 28854095]

O’Malley R et al. Porphyria: often discussed but too often missed. *Pract Neurol.* 2018;18:352. [PMID: 29540448]

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 Stözel U et al. Clinical guide and update on porphyrias. *Gastroenterology.* 2019;157:365. [PMID: 31085196]
 Zhao L et al. Therapeutic strategies for acute intermittent porphyria. *Intractable Rare Dis Res.* 2020;9:205. [PMID: 33139979]

DOWN SYNDROME

ESSENTIALS OF DIAGNOSIS

- ▶ Typical craniofacial features (flat occiput, epicanthal folds, large tongue).
- ▶ Intellectual disability.
- ▶ Congenital heart disease (eg, atrioventricular canal defects) in 50% of patients.
- ▶ Alzheimer dementia in early-to-mid adulthood.
- ▶ Three copies of chromosome 21 (trisomy 21) or a chromosome rearrangement that results in three copies of a region of the long arm of chromosome 21.

► General Considerations

Nearly 0.5% of all human conceptions are trisomic for chromosome 21. Because of increased fetal mortality, birth incidence of Down syndrome is 1 per 700 but varies from 1 per 1000 in young mothers to more than three times as frequent in women of advanced maternal age. The presence of a fetus with Down syndrome can be detected in many pregnancies in the first or early second trimester through screening maternal serum for alpha-fetoprotein and other biomarkers (“multiple marker screening”) and by detecting increased nuchal thickness and underdevelopment of the nasal bone on ultrasonography. Prenatal diagnosis with high sensitivity and specificity can be achieved by assaying fetal DNA that is circulating in maternal blood. The chance of bearing a child with Down syndrome increases exponentially with the age of the mother at conception and begins a marked rise after age 35. By age 45 years, the odds of having an affected child are as high as 1 in 40. The risk of other conditions associated with trisomy also increases, because of the predisposition of older oocytes to nondisjunction during meiosis. There is little risk of trisomy associated with increased paternal age. However, older men do have an increased risk of fathering a child with a new autosomal dominant condition. Because there are so many distinct conditions, though, the chance of fathering an offspring with any given one is extremely small.

► Clinical Findings

A. Symptoms and Signs

Down syndrome is usually diagnosed at birth on the basis of the typical craniofacial features, hypotonia, and single palmar crease. Several serious problems that may be evident at birth or may develop early in childhood include duodenal atresia, congenital heart disease

(especially atrioventricular canal defects), and hematologic malignancy. The intestinal and cardiac anomalies usually respond to surgery. A transient neonatal leukemia generally responds to conservative management. The incidences of both acute lymphoblastic and myeloid leukemias are increased in childhood. Intelligence varies across a wide spectrum. Many people with Down syndrome do well in sheltered workshops and group homes, but few achieve full independence in adulthood. Other frequent complications include atlanto-axial instability, celiac disease, frequent infections due to immune deficiency, and hypothyroidism. An Alzheimer-like dementia usually becomes evident in the fourth or fifth decade. Patients with Down syndrome who survive childhood and who develop dementia have a reduced life expectancy; on average, they live to about age 55 years.

B. Laboratory Findings

Cytogenomic analysis should always be performed—even though most patients will have simple trisomy for chromosome 21—to detect unbalanced translocations; such patients may have a parent with a balanced translocation, and there will be a substantial recurrence risk of Down syndrome in future offspring of that parent and potentially that parent's relatives.

Treatment

Duodenal atresia should be treated surgically. Congenital heart disease should be treated as in any other patient. Effective treatment does no long-term harm to neurodevelopment. As yet, no medical treatment has been proven to affect the neurodevelopmental or the neurodegenerative aspects. Based on the glutamatergic hypothesis for Alzheimer disease, studies have been initiated examining the potential benefit of the N-methyl-D-aspartate receptor antagonist memantine.

When to Refer

- For comprehensive evaluation of infants to investigate congenital heart disease, hematologic malignancy, and duodenal atresia.
- For genetic counseling of the parents.
- For signs of dementia in an adult patient.

When to Admit

A young patient should be hospitalized for failure to thrive, regurgitation, or breathlessness.

Neil N et al. Communication intervention for individuals with Down syndrome: systematic review and meta-analysis. *Dev Neurorehabil*. 2018;21:1. [PMID: 27537068]
Ross WT et al. Care of the adult patient with Down syndrome. *South Med J*. 2014;107:715. [PMID: 25365441]

FAMILIAL HYPERCHOLESTEROLEMIA



ESSENTIALS OF DIAGNOSIS

- Elevated serum total cholesterol and LDL cholesterol.
- Autosomal dominant inheritance.
- Mutation in *LRL*, *PCSK9*, or *APOB*.

General Considerations

Familial hypercholesterolemia (FH) is a group of autosomal dominant conditions that result in elevated low-density lipoprotein (LDL) levels in the blood. High LDL predisposes to atherosclerosis, which in turn leads to premature myocardial infarction or stroke. The incidence of these serious complications increases with age and when associated with the other common predispositions to atherosclerosis, such as smoking and hypertension. About 1 in 500 people in the United States have FH; worldwide, the prevalence is about 10 million. Only about 15% of people with FH are diagnosed and even fewer are treated effectively.

Clinical Findings

A. Symptoms and Signs

Yellow lipid deposits appear on tendons, especially the Achilles (tendon xanthoma).

B. Laboratory Findings

Total serum cholesterol with the LDL component is particularly high. A detailed family history and genetic testing should be obtained when individuals are younger than 40 years with an LDL level greater than 200 mg/mL and for individuals older than 40 years with a level greater than 250 mg/mL.

Prevention

In most instances, the elevated LDL is inherited as an autosomal dominant trait. An affected individual in all likelihood inherited FH from one parent, and each of his or her children has a 50/50 chance of inheriting FH. In uncommon cases, both parents have a mutation in the LDL receptor and one-quarter of their children, on average, will inherit two mutant alleles and have homozygous FH, which is a much more serious disease with manifestations in childhood.

Mutations in the following four genes can cause FH: (1) *LDLR*, which encodes the LDL receptor located on the surface of cells and responsible for moving LDL into the cell for metabolism; the most common mutant gene in FH; (2) *APOB*, which encodes a component of LDL and mutations inhibit binding to LDL receptor; (3) *PCSK9*, which

Badeau M et al. Genomics-based non-invasive prenatal testing for detection of fetal chromosomal aneuploidy in pregnant women. *Cochrane Database Syst Rev*. 2017;11:CD011767. [PMID: 29125628]

Coppède F. Risk factors for Down syndrome. *Arch Toxicol*. 2016;90:2917. [PMID: 27600794]

Gandy KC et al. The relationship between chronic health conditions and cognitive deficits in children, adolescents, and young adults with Down syndrome: a systematic review. *PLoS One*. 2020;15:e0239040. [PMID: 32915911]

encodes a protein that normally reduces production of LDL receptors, so mutations actually protect from hypercholesterolemia; and (4) *ARH*, which requires mutations in both alleles (autosomal recessive inheritance) to cause FH.

► Treatment

Statins, usually at high doses, can reduce LDL levels, occasionally to acceptable levels (see Table 28–3). The earlier in life that treatment is begun, the better the outcome in reducing mortality from atherosclerosis. In homozygous FH, if high-dose statins do not reduce LDL sufficiently, treatment with a monoclonal antibody (eg, alirocumab and evolocumab) that blocks the action of the *PCSK9* enzyme (which inactivates hepatic receptors that transport LDL into the liver for metabolism) can be an expensive adjunct to standard therapy (Chapter 28, Lipid Disorders). If all else fails, then plasmapheresis is needed to reduce LDL.

Another important need in effective management is to screen relatives who are at risk, certainly by measuring LDL levels, but increasingly by identifying the mutation in the family and utilizing that for screening.

► When to Refer

- For comprehensive evaluation of infants for their lipid profile.
- For genetic counseling of the patient, his or her parents, siblings, and offspring.
- For signs of atherosclerotic cardiovascular disease.

► When to Admit

For signs or symptoms of acute arterial occlusive events.

Kramer AI et al. Estimating the prevalence of familial hypercholesterolemia in acute coronary syndrome: systematic review and meta-analysis. *Can J Cardiol*. 2019;35:1322. [PMID: 31500889]
Louter L et al. Cascade screening for familial hypercholesterolemia: practical consequences. *Atheroscler Suppl*. 2017;30:77. [PMID: 29096865]

Rosenson RS. CETP inhibition improves the lipid profile but has no effect on clinical cardiovascular outcomes in high-risk patients. *Evid Based Med*. 2017;22:184. [PMID: 28844064]

Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol*. 2019;16:155. [PMID: 30420622]

FRAGILE X SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Expanded trinucleotide repeat (> 200) in the *FMR1* gene.
- ▶ **Males:** mental impairment and autism; large testes after puberty.
- ▶ **Females:** learning disabilities or mental impairment; premature ovarian failure.
- ▶ Late-onset tremor and ataxia in males and females with moderate trinucleotide repeat (55–200) expansion (premutation carriers).

► Clinical Findings

A. Symptoms and Signs

This X-linked condition accounts for more cases of mental impairment in males than any condition except Down syndrome; about 1 in 4000 males is affected. The central nervous system phenotype includes autism spectrum, impulsivity and aggressiveness, and repetitive behaviors. The condition also affects intellectual function in females, although less severely and about 50% less frequently than in males. Affected (heterozygous) young women show no physical signs other than early menopause, but they may have learning difficulties, anxiety, sensory issues, or frank impairment. Affected males show macro-orchidism (enlarged testes) after puberty, large ears and a prominent jaw, a high-pitched voice, autistic characteristics, and mental impairment. Some males show evidence of a mild connective tissue defect, with joint hypermobility and mitral valve prolapse.

Women who are premutation carriers (55–200 CGG repeats) are at increased risk for premature ovarian insufficiency (FXPOI) and mild cognitive abnormalities. Male and female premutation carriers are at risk for mood and anxiety disorders and the development of tremor and ataxia beyond middle age (fragile-X tremor-ataxia syndrome, FXTAS). Changes in the cerebellar white matter may be evident on MRI before symptoms appear. Because of the relatively high prevalence of premutation carriers in the general population (1/130–1/600), older people in whom any of these behavioral or neurologic problems develop should undergo testing of the *FMR1* locus.

B. Laboratory Findings

The first marker for this condition was a small gap, or fragile site, evident near the tip of the long arm of the X chromosome. Subsequently, the condition was found to be due to expansion of a trinucleotide repeat (CGG) near a gene called *FMR1*. All individuals have some CGG repeats in this location, but as the number increases beyond 52, the chances of further expansion during spermatogenesis or oogenesis increase.

Being born with one *FMR1* allele with 200 or more repeats results in mental impairment in most men and in about 60% of women. The more repeats, the greater the likelihood that further expansion will occur during gametogenesis; this results in anticipation, in which the disorder can worsen from one generation to the next.

► Prevention

DNA diagnosis for the number of repeats has supplanted cytogenetic analysis for both clinical and prenatal diagnosis. This should be done on any male or female who has unexplained mental impairment. Newborn screening based on hypermethylation of the *FMR1* gene is being considered as a means of early detection and intervention.

► Treatment

Several treatments that address the imbalances in neurotransmission have been developed based on the mouse model and are in clinical trials. Valproic acid may reduce

symptoms of hyperactivity and attention deficit, but standard therapies should be tried first.

► When to Refer

- For otherwise unexplained mental impairment or learning difficulties in boys and girls.
- For otherwise unexplained tremor or ataxia in middle-aged individuals.
- For premature ovarian failure.
- For genetic counseling.

Fink DA et al. Fragile X associated primary ovarian insufficiency (FXPOI): case report and literature review. *Front Genet*. 2018;9:529. [PMID: 30542367]

Huang G et al. Long noncoding RNA can be a probable mechanism and novel target for diagnosis and therapy in fragile X syndrome. *Front Genet*. 2019;10:466. [PMID: 31191598]

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Salcedo-Arellano MJ et al. Fragile X syndrome and associated disorders: clinical aspects and pathology. *Neurobiol Dis*. 2020; 136:104740. [PMID: 31927143]

GAUCHER DISEASE



ESSENTIALS OF DIAGNOSIS

- Deficiency of beta-glucocerebrosidase.
- Anemia and thrombocytopenia.
- Hepatosplenomegaly.
- Pathologic fractures.

► Clinical Findings

A. Symptoms and Signs

Gaucher disease has an autosomal recessive pattern of inheritance. A deficiency of beta-glucocerebrosidase causes an accumulation of sphingolipid within phagocytic cells throughout the body. Anemia and thrombocytopenia are common and may be symptomatic; both are due primarily to hypersplenism, but marrow infiltration with Gaucher cells may be a contributing factor. The abdomen can become painfully distended due to enlargement of the liver and spleen.

Cortical erosions of bones, especially the vertebrae and femur, are due to local infarctions, but the mechanism is unclear. Episodes of bone pain (termed “crises”) are reminiscent of those in sickle cell disease. A hip fracture in a patient of any age with a palpable spleen—especially in a Jewish person of Eastern European origin—suggests the possibility of Gaucher disease. Peripheral neuropathy may develop in patients.

Patients with Gaucher disease and heterozygous carriers of a mutation in *GBA* are at increased risk for early-onset Parkinson disease and dementia with Lewy bodies.

Two uncommon forms of Gaucher disease, called type II and type III, involve neurologic accumulation of

sphingolipid and a variety of neurologic problems. Type II is of infantile onset and has a poor prognosis. Heterozygotes for Gaucher disease are at increased risk for developing Parkinson disease.

B. Laboratory Findings

Bone marrow aspirates reveal typical Gaucher cells, which have an eccentric nucleus and periodic acid-Schiff (PAS)-positive inclusions, along with wrinkled cytoplasm and inclusion bodies of a fibrillar type. In addition, the serum acid phosphatase is elevated. Definitive diagnosis requires the demonstration of deficient glucocerebrosidase activity in leukocytes. Hundreds of mutations have been found to cause Gaucher disease and some are highly predictive of the neuropathic forms. Thus, mutation detection, especially in a young person, is of potential value. Only four mutations in glucocerebrosidase account for more than 90% of the disease among Ashkenazi Jews, in whom the carrier frequency is 1:15.

► Prevention

Gaucher disease is the most common lysosomal storage disorder. Most clinical complications can be prevented by early institution of enzyme replacement therapy. Carrier screening, especially among Ashkenazi Jews, detects those couples at 25% risk of having an affected child. Prenatal diagnosis through mutation analysis is feasible. Because of an increased risk of malignancy, especially plasma cell myeloma and other hematologic cancers, regular screening of adults with Gaucher disease is warranted.

► Treatment

A recombinant form of the enzyme glucocerebrosidase (imiglucerase) for intravenous administration on a regular basis reduces total body stores of glycolipid and improves orthopedic and hematologic manifestations. Unfortunately, the neurologic manifestations of types II and III have not improved with enzyme replacement therapy. The major drawback is the exceptional cost of imiglucerase, which can exceed \$300,000 per year for a severely affected adult patient. Eliglustat tartrate is an oral inhibitor of glucosylceramide synthase and reduces the compound that accumulates; while still quite expensive, this approach eliminates the need for frequent intravenous infusions. Early treatment of affected children normalizes growth and bone mineral density and improves liver and spleen size, anemia, and thrombocytopenia. In adults with thrombocytopenia due to splenic sequestration, enzyme replacement often obviates the need for splenectomy.

Biegstraaten M et al. Management goals for type 1 Gaucher disease: an expert consensus document from the European working group on Gaucher disease. *Blood Cells Mol Dis*. 2018;68: 203. [PMID: 28274788]

Blumenreich S et al. Lysosomal storage disorders shed light on lysosomal dysfunction in Parkinson's disease. *Int J Mol Sci*. 2020;21:4966. [PMID: 32674335]

Nabizadeh A et al. The clinical efficacy of imiglucerase versus eliglustat in patients with Gaucher's disease type 1: a systematic review. *J Res Pharm Pract*. 2018;7:171. [PMID: 30622983]

- Roshan Lal T et al. The spectrum of neurological manifestations associated with Gaucher disease. *Diseases*. 2017;5:E10. [PMID: 28933363]
- Starosta RT et al. Liver involvement in patients with Gaucher disease types I and III. *Mol Genet Metab Rep*. 2020;22:100564. [PMID: 32099816]

DISORDERS OF HOMOCYSTEINE METABOLISM



ESSENTIALS OF DIAGNOSIS

- ▶ Hyperhomocysteinemia: more vascular disease but lowering homocysteine levels is not helpful.
- ▶ Homocystinuria: Marfan-like habitus, ectopia lentis, mental impairment, thromboses.
- ▶ Elevated homocysteine in the urine or plasma.

► General Considerations

Patients with clinical and angiographic evidence of coronary artery disease and cerebrovascular and peripheral vascular diseases tend to have higher levels of plasma homocysteine than persons without these vascular diseases. Although this effect was initially thought to be due at least in part to heterozygotes for cystathione beta-synthase deficiency (see below), there is little supporting evidence. Rather, an important factor leading to hyperhomocysteinemia is folate deficiency. Pyridoxine (vitamin B₆) and vitamin B₁₂ are also important in the metabolism of methionine, and deficiency of any of these vitamins can lead to accumulation of homocysteine. A number of genes influence utilization of these vitamins and can predispose to deficiency. For example, having one copy—and especially two copies—of an allele that causes thermolability of methylene tetrahydrofolate reductase predisposes people to elevated fasting homocysteine levels. Both nutritional and most genetic deficiencies of these vitamins can be corrected by dietary supplementation of folic acid and, if serum levels are low, vitamins B₆ and B₁₂. In the United States, cereal grains are fortified with folic acid. However, therapy with B vitamins and folate lowers homocysteine levels significantly but does not reduce the risk of either venous thromboembolism or complications of coronary artery disease. The role of lowering homocysteine as primary prevention for cardiovascular disease has received modest direct support in clinical trials. Hyperhomocysteinemia occurs with end-stage chronic kidney disease. In the general population, elevated homocysteine correlates with cognitive impairment.

► Clinical Findings

A. Symptoms and Signs

Homocystinuria in its classic form is caused by cystathione beta-synthase deficiency and exhibits autosomal recessive inheritance. This results in extreme elevations of plasma and urinary homocysteine levels, a basis for

diagnosis of this disorder. Homocystinuria is similar in certain superficial aspects to Marfan syndrome, since patients may have a similar body habitus and ectopia lentis is almost always present. However, mental impairment is often present in homocystinuria, and the cardiovascular events are those of repeated venous and arterial thromboses whose precise cause remains obscure. Thus, the diagnosis should be suspected in patients in the second and third decades of life who have arterial or venous thromboses without other risk factors. Bone mineral density is reduced in untreated patients. Life expectancy is reduced, especially in untreated and pyridoxine-unresponsive patients; myocardial infarction, stroke, and pulmonary embolism are the most common causes of death. This condition is diagnosed by newborn screening for hypermethioninemia; however, pyridoxine-responsive infants may not be detected. In addition, homozygotes for a common mutant allele, p.I278T, show marked clinical variability, with some unaffected as adults.

B. Laboratory Findings

Although many mutations have been identified in the cystathione beta-synthase gene, amino acid analysis of plasma remains the most appropriate diagnostic test. Patients should be studied after they have been off folate or pyridoxine supplementation for at least 1 week. Relatively few laboratories currently provide highly reliable assays for homocysteine. Processing of the specimen is crucial to obtain accurate results. The plasma must be separated within 30 minutes; otherwise, blood cells release the amino acid and the measurement will then be artificially elevated.

► Prevention

Prenatal diagnosis and termination of the affected pregnancy are the only current way to prevent the occurrence of CBS-deficient homocystinuria.

► Treatment

About 50% of patients have a form of cystathione beta-synthase deficiency that improves biochemically and clinically through pharmacologic doses of pyridoxine (50–500 mg orally daily) and folate (5–10 mg orally daily). For these patients, treatment that begins in infancy can prevent impairment and the other clinical problems. Patients who do not respond to pyridoxine must be treated with a dietary reduction in methionine and supplementation of cysteine, again beginning in infancy. The vitamin betaine is also useful in reducing plasma methionine levels by facilitating a metabolic pathway that bypasses the defective enzyme.

Patients with classic homocystinuria who have suffered venous thrombosis receive anticoagulation therapy, but there are no studies to support prophylactic use of warfarin or antiplatelet agents.

Gales A et al. Adolescence/adult onset MTHFR deficiency may manifest as isolated and treatable distinct neuro-psychiatric syndromes. *Orphanet J Rare Dis*. 2018;13:29. [PMID: 29391032]

Sacharow SJ et al. Homocystinuria Caused by Cystathione Beta-Synthase Deficiency. In: Adam MP et al (editors). GeneReviews®. 2004 Jan 15 [Updated 2017]. [PMID: 20301697] Weber Hoss GR et al. Classical homocystinuria: a common inborn error of metabolism? An epidemiological study based on genetic databases. Mol Genet Genomic Med. 2020;8:e1214. [PMID: 32232970]

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Ross JL et al. Androgen treatment effects on motor function, cognition, and behavior in boys with Klinefelter syndrome. J Pediatr. 2017;185:193. [PMID: 28285751]

Skakkebaek A et al. Quality of life in men with Klinefelter syndrome: the impact of genotype, health, socioeconomics, and sexual function. Genet Med. 2018;20:214. [PMID: 28726803]

KLINEFELTER SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Males with hypergonadotropic hypogonadism and small testes.
- ▶ 47,XXY karyotype.

► Clinical Findings

A. Symptoms and Signs

Boys with an extra X chromosome are normal in appearance before puberty; thereafter, they have disproportionately long legs and arms, sparse body hair, a female escutcheon, gynecomastia, and small testes. Infertility is due to azoospermia; the seminiferous tubules are hyalinized. The incidence is 1 in 660 newborn males, but the diagnosis is often not made until a man is evaluated for inability to conceive. Intellectual disability is somewhat more common than in the general population. Many men with Klinefelter syndrome have language-based learning problems. However, their intelligence usually tests within the broad range of normal. As adults, detailed psychometric testing may reveal a deficiency in executive skills. The risk of osteoporosis, breast cancer, and diabetes mellitus is much higher in men with Klinefelter syndrome than in 46,XY men.

B. Laboratory Findings

Low serum testosterone is common. The karyotype is typically 47,XXY, but other sex chromosome anomalies cause variations of Klinefelter syndrome.

► Prevention

Screening for cancer (especially of the breast), deep venous thrombosis, and glucose intolerance is indicated.

► Treatment

Treatment with testosterone after puberty is advisable but will not restore fertility. However, men with Klinefelter syndrome have had mature sperm aspirated from their testes and injected into oocytes, resulting in fertilization. After the blastocysts have been implanted into the uterus of a partner, conception has resulted. But, men with Klinefelter syndrome do have an increased risk for aneuploidy in sperm, and therefore, genomic analysis of a blastocyst should be considered before implantation.

MARFAN SYNDROME



ESSENTIALS OF DIAGNOSIS

- ▶ Disproportionately tall stature, thoracic deformity, and joint laxity or contractures.
- ▶ Ectopia lentis and myopia.
- ▶ Aortic root dilation and dissection; mitral valve prolapse.
- ▶ Mutation in *FBN1*, the gene encoding fibrillin-1.

► General Considerations

Marfan syndrome, a systemic connective tissue disease, has an autosomal dominant pattern of inheritance. It is characterized by abnormalities of the skeletal, ocular, and cardiovascular systems; spontaneous pneumothorax; dural ectasia; and striae atrophicae. Of most concern is disease of the ascending aorta, which begins as a dilated aortic root. Histology of the aorta shows diffuse medial degeneration. Mitral valve leaflets are also abnormal and mitral prolapse and regurgitation may be present, often with elongated chordae tendineae, which on occasion may rupture.

► Clinical Findings

A. Symptoms and Signs

Affected patients are typically tall, with particularly long arms, legs, and digits (arachnodactyly). However, there can be wide variability in the clinical presentation. Commonly, scoliosis and anterior chest deformity, such as pectus excavatum, are found. Ectopia lentis is present in about half of patients; severe myopia is common and retinal detachment can occur. Mitral valve prolapse is seen in about 85% of patients. Aortic root dilation is common and leads to aortic regurgitation or dissection with rupture. To diagnose Marfan syndrome, people with an affected relative need features in at least two systems. People with no family history need features in the skeletal system, two other systems, and one of the major criteria of ectopia lentis, dilation of the aortic root, or aortic dissection. Patients with homocystinuria due to cystathione beta-synthase deficiency also have dislocated lenses, tall, disproportionate stature, and thoracic deformity. They tend to have below normal intelligence, stiff joints, and a predisposition to arterial and venous occlusive disease. Males with Klinefelter syndrome do not show the typical ocular or cardiovascular features of Marfan syndrome and are generally sporadic occurrences in the family.

B. Laboratory Findings

Mutations in the fibrillin gene (*FBN1*) on chromosome 15 cause Marfan syndrome. Nonetheless, no simple laboratory test is available to support the diagnosis in questionable cases because related conditions may also be due to defects in fibrillin. The nature of the *FBN1* mutation has little predictive value in terms of prognosis. The pathogenesis of Marfan syndrome involves aberrant regulation of transforming growth factor (TGF)-beta activity. Mutations in either of two receptors for TGF-beta (TGFBR1 and TGFBR2) can cause conditions that resemble Marfan syndrome in terms of aortic aneurysm and dissection and autosomal dominant inheritance. Mutations in more than two dozen other genes can predispose adults to thoracic aortic aneurysm and dissection.

► Prevention

There is prenatal and presymptomatic diagnosis for patients in whom the molecular defect in *FBN1* has been found.

► Treatment

Children with Marfan syndrome require regular ophthalmologic surveillance to correct visual acuity and thus prevent amblyopia, and annual orthopedic consultation for diagnosis of scoliosis at an early enough stage so that bracing might delay progression. Patients of all ages require echocardiography at least annually to monitor aortic root diameter and mitral valve function. Long-term beta-adrenergic blockade, titrated to individual tolerance but enough to produce a negative inotropic effect (atenolol, 1–2 mg/kg orally daily), retards the rate of aortic dilation. While inhibition of the TGF-beta signaling pathway through angiotensin receptor blockade (ARB) in mice with Marfan syndrome is highly effective, ARB treatment in humans is no more effective than beta-adrenergic blockade. Calcium channel blockers, once used as a substitute for beta-blockade, are detrimental to the aorta. Restriction from vigorous physical exertion protects from aortic dissection. Prophylactic replacement of the aortic root with a composite graft when the diameter reaches 45–50 mm in an adult (normal: less than 40 mm) prolongs life. Earlier prophylactic surgery should be considered when there is a strong family history of aortic dissection or when the diameter of the aortic root increases more than 3–4 mm per year. A valve-sparing procedure resuspends the patient's native aortic valve inside a graft that replaces the aneurysmal sinuses of Valsalva and ascending aorta, thus avoiding the need for lifelong anticoagulation. Women with Marfan syndrome are at heightened risk for aortic dissection in the peripartum and postpartum periods. Having an aortic root dimension greater than 40 mm should prompt consideration for prophylactic, valve-sparing aortic repair before undertaking a pregnancy.

► Prognosis

People with Marfan syndrome who are untreated commonly die in the fourth or fifth decade from aortic dissection or heart failure secondary to aortic or mitral regurgitation.

However, because of earlier diagnosis, lifestyle modifications, beta-adrenergic blockade, and prophylactic aortic and mitral valve surgery, life expectancy has increased by several decades.

Prophylactic treatment of cardiovascular disease can lead to a near-normal life expectancy. However, with the longer life expectancy, serious comorbidities that were previously infrequent are now more common. These comorbidities include obstructive sleep apnea, cardiomyopathy, aneurysms and dissections of the abdominal aorta and peripheral arteries, neurologic problems related to dural ectasia, and degenerative arthritis.

► When to Refer

- For detailed ophthalmologic examination.
- For at least annual cardiologic evaluation.
- For moderate scoliosis.
- For pregnancy in a woman with Marfan syndrome.
- For genetic counseling.

► When to Admit

Any patient with Marfan syndrome in whom severe or unusual chest pain develops should be hospitalized to exclude pneumothorax and aortic dissection.

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HEREDITARY HEMORRHAGIC TELANGIECTASIA

ESSENTIALS OF DIAGNOSIS

- 
- Recurrent epistaxis.
 - Mucocutaneous telangiectases.
 - Visceral arteriovenous malformations (especially lung, liver, brain, bowel).

► Clinical Findings

A. Symptoms and Signs

Hereditary hemorrhagic telangiectasia (HHT), formerly termed “Osler-Weber-Rendu syndrome,” is an autosomal

dominant disorder of development of the vasculature. Epistaxis may begin in childhood or later in adolescence. Punctate telangiectases of the lips, tongue, fingers, and skin generally appear in later childhood and adolescence. Arteriovenous malformations (AVMs) can occur at any age in the brain, lungs, and liver. Bleeding from the gastrointestinal tract is due to mucosal vascular malformations and usually is not a problem until mid-adult years or later. Pulmonary AVMs can cause hypoxemia (with peripheral cyanosis, dyspnea, and clubbing) and right-to-left shunting (with embolic stroke or brain abscess). The criteria for diagnosis require presence of three of the following four features: (1) recurrent epistaxis, (2) visceral AVMs, (3) mucocutaneous telangiectases, and (4) being the near relative of a clearly affected individual. Mutation analysis can be used for presymptomatic diagnosis or exclusion of the worry of HHT.

B. Laboratory Findings

MR or CT arteriography detects AVMs. Mutations in at least five genes can cause HHT. Three have been identified, and molecular analysis to identify them is available; these mutations in *ENG*, *ALK1*, and *SMAD4* account for about 87% of families with HHT. When the familial mutation is known, molecular testing is far more cost effective than repeated clinical screening of relatives who are at risk.

► Prevention

Embolization of pulmonary AVMs with wire coils or other occlusive devices reduces the risk of stroke and brain abscess. Treatment of brain AVMs reduces the risk of hemorrhagic stroke. All patients with HHT with evidence of a pulmonary shunt should practice routine endocarditis prophylaxis (see Table 33–5). All intravenous lines (except those for transfusion of red blood cells and radiographic contrast) should have an air-filter to prevent embolization of an air bubble. Prenatal diagnosis through mutation detection is possible.

► Treatment

All patients in whom the diagnosis of HHT is considered should have an MRI of the brain with contrast. A contrast echocardiogram will detect most pulmonary AVMs when “bubbles” appear on the left side of the heart after 3–6 cardiac cycles. A positive contrast echocardiogram should be followed by a high-resolution CT angiogram for localization of pulmonary AVMs. Patients who have AVMs with a feeding artery of 2 mm diameter or greater should undergo embolization. After successful embolization of all treatable pulmonary AVMs, the CT angiogram should be repeated in 6 months and 3 years. A person with a negative contrast echocardiogram should have the test repeated every 5 years. Any person with a pulmonary AVM, even an embolized one, should utilize routine endocarditis prophylaxis. Several studies suggest that treatment with anti-estrogenic agents (eg, tamoxifen), thalidomide or its relatives, or anti-vascular endothelial growth factor agents (eg, bevacizumab) can reduce epistaxis and gastrointestinal bleeding and improve hepatic shunting. However, two randomized, controlled clinical trials of intranasal bevacizumab therapy failed to show an improvement in epistaxis.

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- Chick JFB et al. A survey of pulmonary arteriovenous malformation screening, management, and follow-up in Hereditary Hemorrhagic Telangiectasia Centers of Excellence. *Cardiovasc Interv Radiol.* 2017;40:1003. [PMID: 28188364]
- Faughnan ME et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med.* 2020;173:989. [PMID: 32894695]
- Halderman AA et al. Bevacizumab for epistaxis in hereditary hemorrhagic telangiectasia: an evidence-based review. *Am J Rhinol Allergy.* 2018;32:258. [PMID: 29745243]
- Jackson SB et al. Gastrointestinal manifestations of Hereditary Hemorrhagic Telangiectasia (HHT): a systematic review of the literature. *Dig Dis Sci.* 2017;62:2623. [PMID: 28836046]
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Orthopedic Disorders & Sports Medicine

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C. Benjamin Ma, MD

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Musculoskeletal problems account for about 10–20% of outpatient primary care clinical visits. Orthopedic problems can be classified as traumatic (ie, injury-related) or atraumatic (ie, degenerative or overuse syndromes) as well as acute or chronic. The history and physical examination are sufficient in most cases to establish the working diagnosis; the mechanism of injury is usually the most helpful part of the history in determining the diagnosis.

SHOULDER

1. Subacromial Impingement Syndrome



ESSENTIALS OF DIAGNOSIS

- ▶ Shoulder pain with overhead motion.
- ▶ Night pain with sleeping on shoulder.
- ▶ Numbness and pain radiation below the elbow are usually due to cervical spine disease.

► General Considerations

The shoulder is a ball and socket joint. The socket is very shallow, however, which enables this joint to have the most motion of any joint. The shoulder, therefore, relies heavily on the surrounding muscles and ligaments to provide stability. The subacromial impingement syndrome describes a collection of diagnoses that cause mechanical inflammation in the subacromial space. Causes of impingement syndrome can be related to muscle strength imbalances, poor scapula control, rotator cuff tears, subacromial bursitis, and bone spurs.

With any shoulder problem, it is important to establish the patient's hand dominance, occupation, and recreational activities because shoulder injuries may present differently depending on the demands placed on the shoulder joint. Baseball pitchers with impingement syndrome may complain of pain while throwing, while older adults with even full-thickness rotator cuff tears may not complain of any pain because the demands on the joint are lower.

► Clinical Findings

A. Symptoms and Signs

Subacromial impingement syndrome classically presents with one or more of the following: pain with overhead activities, nocturnal pain with sleeping on the shoulder, or pain on internal rotation (eg, putting on a jacket or bra). On inspection, there may be appreciable atrophy in the supraspinatus or infraspinatus fossa. The patient with impingement syndrome can have mild scapula winging or "dyskinesis." The patient often has a rolled-forward shoulder posture or head-forward posture. On palpation, the patient can have tenderness over the anterolateral shoulder at the edge of the greater tuberosity. The patient may lack full active range of motion (Table 41–1) but should have preserved passive range of motion. Impingement symptoms can be elicited with the Neer and Hawkins impingement signs (Table 41–1).

B. Imaging

The following four radiographic views should be ordered to evaluate subacromial impingement syndrome: the anteroposterior (AP) scapula, the AP acromioclavicular joint, the lateral scapula (scapular Y), and the axillary lateral. The AP scapula view can rule out glenohumeral joint arthritis. The AP acromioclavicular view evaluates the acromioclavicular joint for inferior spurs. The scapula Y view evaluates the acromial shape, and the axillary lateral view visualizes the glenohumeral joint as well and for the presence of os acromiale.

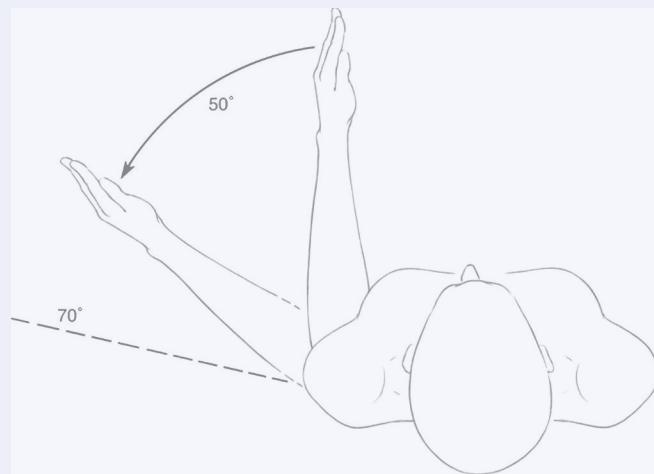
MRI of the shoulder may demonstrate full- or partial-thickness tears or tendinosis. Ultrasound evaluation may demonstrate thickening of the rotator cuff tendons and tendinosis. Tears may also be visualized on ultrasound, although it is more difficult to identify partial tears from small full-thickness tears than on MRI.

► Treatment

A. Conservative

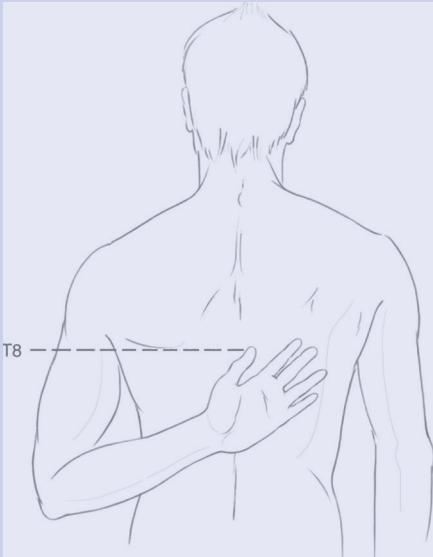
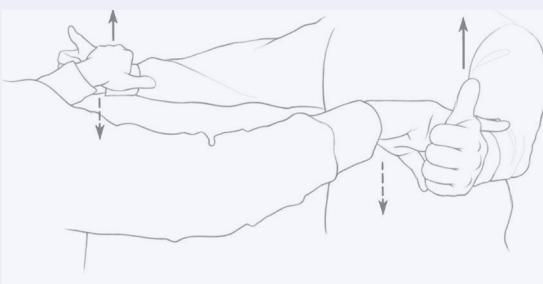
The first-line treatment for impingement syndrome is usually a conservative approach with education, activity modification, and physical therapy exercises.

Table 41–1. Shoulder examination.

Maneuver	Description
Inspection	Check the patient's posture and "SEADS" (swelling, erythema, atrophy, deformity, surgical scars).
Palpation	Include important landmarks: acromioclavicular (AC) joint, long head of biceps tendon, coracoid, and greater tuberosity (supraspinatus insertion).
Range of Motion Testing: Check range of motion actively (patient performs) and passively (clinician performs).	
Flexion	Move the arm forward as high as possible in the sagittal plane.
	
External rotation	Check with the patient's elbow touching their body so that external rotation occurs predominantly at the glenohumeral joint.
	

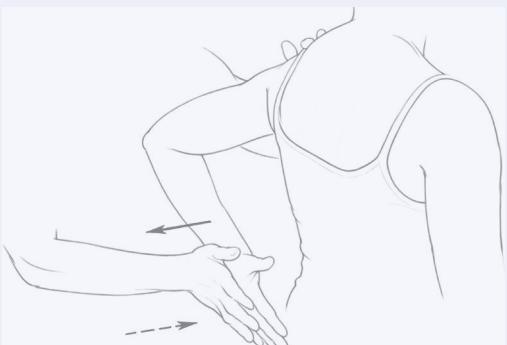
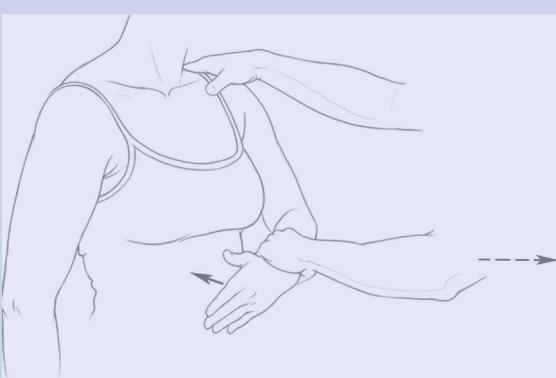
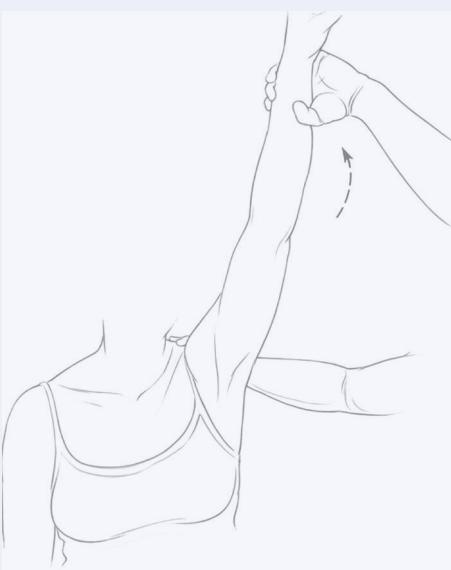
(continued)

Table 41–1. Shoulder examination. (continued)

Maneuver	Description
Internal rotation 	The patient is asked to reach the thumbs as high as possible behind the spine on each side. The clinician can record the highest spinous process that the individual can reach on each side (iliac crest = L4, inferior angle of scapula = T8).
Rotator Cuff Strength Testing Supraspinatus (open can) test 	Perform resisted shoulder abduction at 90 degrees with slight forward flexion to around 45 degrees to test for supraspinatus tendon strength ("open can" test), or with shoulder abduction at 30 degrees and flexion to 30 degrees ("empty can" test).
External rotation 	The patient resists by externally rotating the arms with elbows at his or her side.

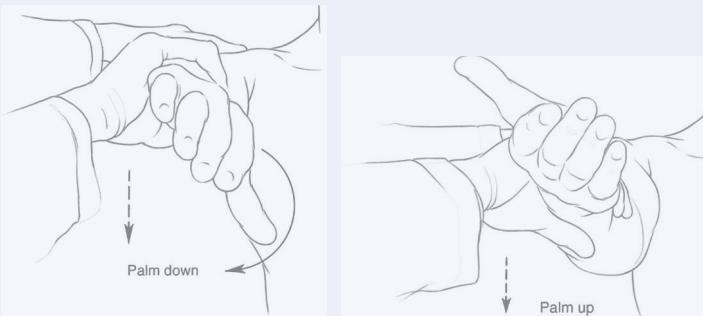
(continued)

Table 41–1. Shoulder examination. (continued)

Maneuver	Description
Internal rotation (lift-off test) 	The clinician pushes the patient's hand toward the back while the patient resists. A positive lift-off indicates subscapularis tendon insufficiency. Positive test: Inability of the patient to hold his or her hand away from the body when reaching toward the small of the back.
Internal rotation (belly-press test) 	A positive belly-press test indicates subscapularis tendon insufficiency. Positive test: Inability to hold the elbow in front of the trunk while pressing down with the hand on the belly.
Impingement Testing	
Neer impingement sign 	Perform by having the clinician flex the shoulder maximally in an overhead position. Positive test: Pain is reproduced with full passive shoulder flexion. Sensitivity is 79%; specificity is 53%.

(continued)

Table 41–1. Shoulder examination. (continued)

Maneuver	Description
Hawkins impingement sign 	Perform with the shoulder forward flexed 90 degrees and the elbow flexed at 90 degrees. The shoulder is then maximally internally rotated to impinge the greater tuberosity on the undersurface of the acromion. Positive test: Pain is reproduced by this maneuver. Sensitivity is 79%; specificity is 59%.
Stability Testing	
Apprehension test 	With persistent anterior instability or a recent dislocation, the patient feels pain or guards when the shoulder is abducted and externally rotated at 90 degrees. With posterior instability, the patient is apprehensive with the shoulder forward flexed and internally rotated to 90 degrees with a posteriorly directed force.
Load and shift test 	Perform to determine shoulder instability by manually translating the humeral head anteriorly and posteriorly in relation to the glenoid. However, this test can be difficult to perform when the patient is not relaxed.
O'Brien test 	Performed to rule out labral cartilage tears that often occur following a shoulder subluxation or dislocation. The test involves flexing the patient's arm to 90 degrees, fully internally rotating the arm so the thumb is facing down (palm down), and adducting the arm to 10 degrees. Once positioned properly, the clinician applies downward force and asks the patient to resist. The test is then repeated in the same position except that the patient has his arm fully supinated (palm up). Positive test: There is pain deep in the shoulder with palm down more than the palm up. The O'Brien test can also be used to identify AC joint pathology. The patient would typically complain equally of pain directly over the AC joint with the palm down or up.

Impingement syndrome can be caused by muscle weakness or tear. Rotator cuff muscle strengthening can alleviate weakness or pain, unless the tendons are seriously compromised, in which case exercises may cause more symptoms. Physical therapy is directed at rotator cuff muscle strengthening, scapula stabilization, and postural exercises. There is no strong evidence supporting the effectiveness of ice and nonsteroidal anti-inflammatory drugs (NSAIDs) as a prolonged therapy. In a Cochrane review, corticosteroid injections produced slightly better relief of symptoms in the short term when compared with placebo. Most patients respond well to conservative treatment.

B. Surgical

Procedures include arthroscopic acromioplasty with coracoacromial ligament release, bursectomy, or debridement or repair of rotator cuff tears. However, the value of acromioplasty alone for rotator cuff problems is not supported by evidence.

► When to Refer

- Failure of conservative treatment over 3 months.
- Young and active patients with impingement due to full-thickness rotator cuff tears.

Consigliere P et al. Subacromial impingement syndrome: management challenges. *Orthop Res Rev*. 2018;10:83. [PMID: 30774463]

Lai CC et al. Effectiveness of stretching exercise versus kinesio-taping in improving length of the pectoralis minor: a systematic review and network meta-analysis. *Phys Ther Sport*. 2019;40:19. [PMID: 31442850]

McFarland EG et al. Clinical faceoff: what is the role of acromioplasty in the treatment of rotator cuff disease? *Clin Orthop Relat Res*. 2018;476:1707. [PMID: 30001291]

Saracoglu I et al. Does taping in addition to physiotherapy improve the outcomes in subacromial impingement syndrome? A systematic review. *Physiother Theory Pract*. 2018; 34:251. [PMID: 29111849]

2. Rotator Cuff Tears



ESSENTIALS OF DIAGNOSIS

- ▶ A common cause of shoulder impingement syndrome after age 40.
- ▶ Difficulty lifting the arm with limited active range of motion.
- ▶ Weakness with resisted strength testing suggests full-thickness tears.
- ▶ Tears can occur following trauma or can be more degenerative.

► General Considerations

Rotator cuff tears can be caused by acute injuries related to falls on an outstretched arm or to pulling on the shoulder.

They can also be related to chronic repetitive injuries with overhead movement and lifting. Partial rotator cuff tears are one of the most common reasons for impingement syndrome. Full-thickness rotator cuff tears are usually more symptomatic and may require surgical treatment. The most commonly torn tendon is the supraspinatus.

► Clinical Findings

A. Symptoms and Signs

Most patients complain of weakness or pain with overhead movement. Night pain is also a common complaint. The clinical findings with rotator cuff tears include those of the impingement syndrome except that with full-thickness rotator cuff tears there may be more obvious weakness noted with light resistance testing of specific rotator cuff muscles. Supraspinatus tendon strength is tested with resisted shoulder abduction at 90 degrees with slight forward flexion to around 45 degrees ("open can" test). Infraspinatus/teres minor strength is tested with resisted shoulder external rotation with shoulder at 0 degrees of abduction and elbow by side. Subscapularis strength is tested with the "lift-off" or "belly-press" tests. The affected patient usually also has positive Neer and Hawkins impingement tests (Table 41–1).

B. Imaging

Recommended radiographs are similar to impingement syndrome: AP scapula (glenohumeral), axillary lateral, supraspinatus outlet, and AP acromioclavicular joint views. The AP scapula view is useful in visualizing rotator cuff tears because degenerative changes can appear between the acromion and greater tuberosity of the shoulder. Axillary lateral views show superior elevation of the humeral head in relation to the center of the glenoid. Supraspinatus outlet views allow evaluation of the shape of the acromion. High-grade acromial spurs are associated with a higher incidence of rotator cuff tears. The AP acromioclavicular joint view evaluates for the presence of acromioclavicular joint arthritis, which can mimic rotator cuff tears, and for spurs that can cause rotator cuff injuries.

MRI is the best method for visualizing rotator cuff tears. The MR arthrogram can show partial or small (less than 1 cm) rotator cuff tears. For patients who cannot undergo MRI testing or when postoperative artifacts limit MRI evaluations, ultrasonography can be helpful.

► Treatment

Partial rotator cuff tears may heal with scarring. Most partial rotator cuff tears can be treated with physical therapy and scapular and rotator cuff muscle strengthening. However, research suggests that 40% of the partial-thickness tears progress to full-thickness tears in 2 years. Physical therapy can strengthen the remaining muscles to compensate for loss of strength and can have high rate of success for chronic tears. Physical therapy is also an option for older sedentary patients. **Full-thickness rotator cuff tears** do not heal well and have a tendency to increase in size with time; 49% of the tears get bigger over an average

of 2.8 years. When tears get larger, they are also associated with worsening pain. Fatty infiltration is a degenerative process where muscle is replaced by fat following injury to the rotator cuff tendons. Fatty infiltration progresses in full-thickness rotator cuff tears and it is a negative prognostic factor for successful surgical treatment. Fatty infiltration is an irreversible process so operative interventions are usually performed when the degree of infiltration is low. Most young active patients with acute, full-thickness tears should be treated with operative fixation. Full-thickness subscapularis tendon tears should undergo surgical repair since untreated tears usually lead to premature osteoarthritis (OA) of the shoulder. Nonetheless, physical therapy is indicated for atraumatic degenerative rotator cuff tears and success can be as high as 70%. That said, long-term (10-year) outcome studies show that surgical repair of rotator cuff tears can result in better outcomes than physical therapy alone.

► When to Refer

- Young and active patients with full-thickness rotator cuff tears.
- Partial tears with greater than 50% involvement and with significant pain.
- Acute rotator cuff tears and loss of function.
- Older and sedentary patients with full-thickness rotator cuff tears who have not responded to nonoperative treatment.
- Full-thickness subscapularis tears.

Allen H et al. Overuse injuries of the shoulder. Radiol Clin North Am. 2019;57:897. [PMID: 31351540]

Amoo-Achampong K et al. Evaluating strategies and outcomes following rotator cuff tears. Shoulder Elbow. 2019;11:4. [PMID: 31019557]

Katthagen JC et al. Improved outcomes with arthroscopic repair of partial-thickness rotator cuff tears: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2018;26:113. [PMID: 28526996]

Moosmayer S et al. At a 10-year follow-up, tendon repair is superior to physical therapy in the treatment of small and medium-sized rotator cuff tears. J Bone Joint Surg Am. 2019;101:1050. [PMID: 31220021]

Piper CC et al. Operative versus nonoperative treatment for the management of full-thickness rotator cuff tears: a systematic review and meta-analysis. J Shoulder Elbow Surg. 2018;27:572. [PMID: 29169957]

3. Shoulder Dislocation & Instability

ESSENTIALS OF DIAGNOSIS

- ▶ Most dislocations (95%) are in the anterior direction.
- ▶ Pain and apprehension with an unstable shoulder that is abducted and externally rotated.
- ▶ Acute shoulder dislocations should be reduced as quickly as possible, using manual relocation techniques if necessary.

► General Considerations

The shoulder is a ball and socket joint, similar to the hip. However, the bony contours of the shoulder bones are much different than the hip. Overall, the joint has much less stability than the hip, allowing greater movement and action. Stabilizing the shoulder joint relies heavily on rotator cuff muscle strength and also scapular control. If patients have poor scapular control or weak rotator cuff tendons or tears, their shoulders are more likely to have instability. Ninety-five percent of the shoulder dislocations/instability occur in the anterior direction. Dislocations usually are caused by a fall on an outstretched and abducted arm. Patients complain of pain and feeling of instability when the arm is in the abducted and externally rotated position. Posterior dislocations are usually caused by falls from a height, epileptic seizures, or electric shocks. Traumatic shoulder dislocation can lead to instability. The rate of repeated dislocation is directly related to the patient's age: patients aged 21 years or younger have a 70–90% risk of redislocation, whereas patients aged 40 years or older have a much lower rate (20–30%). However, once the patient has a second dislocation, the recurrence rate is extremely high, up to 95%, regardless of age. Other risks include male gender and patients with hyperlaxity. Ninety percent of young active individuals who had traumatic shoulder dislocation have labral injuries often described as Bankart lesions when the anterior inferior labrum is torn, which can lead to continued instability. Older patients (over age 55 years) are more likely to have rotator cuff tears or fractures following dislocation. Atraumatic shoulder dislocations are usually caused by intrinsic ligament laxity or repetitive microtrauma leading to joint instability. This is often seen in athletes involved in overhead and throwing sports (eg, in swimmers, gymnasts, and pitchers).

► Clinical Findings

A. Symptoms and Signs

For acute traumatic dislocations, patients usually have an obvious deformity with the humeral head dislocated anteriorly. The patient holds the shoulder and arm in an externally rotated position. The patient has acute pain and deformity. Even after reduction, the patient will continue to have limited range of motion and pain for 4–6 weeks, especially following a first-time shoulder dislocation.

Patients with recurrent dislocations can have less pain with subsequent dislocations. Posterior dislocations can be easily missed because the patient usually holds the shoulder and arm in an internally rotated position, which makes the shoulder deformity less obvious. Patients complain of difficulty pushing open a door.

Atraumatic shoulder instability is usually well tolerated with activities of daily living. Patients usually complain of a “sliding” sensation during exercises or strenuous activities such as throwing. Such dislocations may be less symptomatic and can often undergo spontaneous reduction of the shoulder with pain resolving within days after onset. The clinical examination for shoulder instability includes the apprehension test, the load and shift test, and the O'Brien

test (Table 41–1). Most patients with persistent shoulder instability have preserved range of motion.

B. Imaging

Radiographs for acute dislocations should include a standard trauma series of AP and axillary lateral scapula (glenohumeral) views to determine the relationship of the humerus and the glenoid and to rule out fractures. Orthogonal views are used to identify a posterior shoulder dislocation, which can be missed easily with one AP view of the shoulder. An axillary lateral view of the shoulder can be safely performed even in the acute setting of a patient with a painful shoulder dislocation. A scapula Y view in the acute setting is insufficient to diagnose dislocation. For chronic injuries or symptomatic instability, these recommended radiographic views are helpful to identify bony injuries and Hill-Sachs lesions (indented compression fractures at the posterior-superior part of the humeral head associated with anterior shoulder dislocation). MRI is commonly used to show soft tissue injuries to the labrum and to visualize associated rotator cuff tears. MRI arthrograms better identify labral tears and ligamentous structures. Three-dimensional CT scans are used to determine the significance of bone loss.

Treatment

For **acute dislocations**, manual reductions are usually performed in the emergency department. The shoulder should be reduced as soon as possible. The Stimson procedure is the least traumatic method and is quite effective. The patient lies prone with the dislocated arm hanging off the examination table with a weight applied to the wrist to provide traction for 20–30 minutes. Afterward, gentle medial mobilization can be applied manually to assist the reduction. The shoulder can also be reduced with axial “traction” on the arm with “counter-traction” along the trunk. The patient should be sedated and relaxed. The shoulder can then be gently internally and externally rotated to guide it back into the socket.

Initial treatment of acute shoulder dislocations should include sling immobilization for 2–4 weeks along with pendulum exercises. Early physical therapy can be used to maintain range of motion and strengthening of rotator cuff muscles. Patients can also modify their activities to avoid active and risky sports. For patients with a traumatic incident and unilateral shoulder dislocation, a Bankart lesion is commonly present. Operative intervention is the only treatment that has been shown to decrease recurrence once a patient has a second dislocation. Open and arthroscopic stabilization have very similar outcomes. Repeated dislocations have been shown to increase the risk of arthritis and further bony deterioration.

The treatment of **atraumatic shoulder instability** is different than that of traumatic shoulder instability. Patients with chronic, recurrent shoulder dislocations should be managed with physical therapy and a regular maintenance program, consisting of scapular stabilization and postural and rotator cuff strengthening exercises. Activities may need to be modified. Surgical reconstructions are

less successful for atraumatic shoulder instability than for traumatic shoulder instability. However, patients with recurrent dislocations have much higher incidence of bone loss or biceps pathology when compared to patients with first-time dislocations. They are also more likely to require open surgery with bone augmentation rather than arthroscopic stabilization.

► When to Refer

- Patients who are at risk for second dislocation, such as young patients and certain job holders (eg, police officers, firefighters, and rock climbers), to avoid recurrent dislocation or dislocation while at work.
- Patients who have not responded to a conservative approach or who have chronic instability.

Borbás P et al. Surgical management of chronic high-grade acromioclavicular joint dislocations: a systematic review. *J Shoulder Elbow Surg.* 2019;28:2031. [PMID: 31350107]

Gottlieb M et al. Point-of-care ultrasound for the diagnosis of shoulder dislocation: a systematic review and meta-analysis. *Am J Emerg Med.* 2019;37:757. [PMID: 30797607]

Hasebroock AW et al. Management of primary anterior shoulder dislocations: a narrative review. *Sports Med Open.* 2019;5:31. [PMID: 31297678]

Tamaoki MJ et al. Surgical versus conservative interventions for treating acromioclavicular dislocation of the shoulder in adults. *Cochrane Database Syst Rev.* 2019;10:CD007429. [PMID: 31604007]

4. Adhesive Capsulitis (“Frozen Shoulder”)

ESSENTIALS OF DIAGNOSIS

- ▶ Very painful shoulder triggered by minimal or no trauma.
- ▶ Pain out of proportion to clinical findings during the inflammatory phase.
- ▶ Stiffness during the “freezing” phase and resolution during the “thawing” phase.

► General Considerations

Adhesive capsulitis (“frozen shoulder”) is caused by acute inflammation of the shoulder capsule followed by scarring and remodeling. Injury to the shoulder likely triggers mast cell activation and release of growth factors and cytokines, which lead to metaplasia of fibroblasts into myofibroblasts, resulting in abnormal collagen deposition and fibrosis in the shoulder capsule. Adhesive capsulitis is seen commonly in patients aged 40–65 years old, and it occurs more often in women than men, especially in perimenopausal women or in patients with endocrine disorders, such as diabetes mellitus or thyroid disease. There is higher incidence of adhesive capsulitis following shoulder trauma (such as surgery) or breast cancer care (such as mastectomy), which may create a pro-inflammatory condition in the shoulder. Adhesive capsulitis is a self-limiting but very debilitating disease.

► Clinical Findings

A. Symptoms and Signs

Patients usually present with a painful shoulder that has a limited range of motion with both passive and active movements. A useful clinical sign is limitation of movement of external rotation with the elbow by the side of the trunk (Table 41–1). Strength is usually normal but it can appear diminished when the patient is in pain.

There are three phases: the inflammatory phase, the freezing phase, and the thawing phase. During the inflammatory phase, which usually lasts 4–6 months, patients complain of a very painful shoulder without obvious clinical findings to suggest trauma, fracture, or rotator cuff tear. During the “freezing” phase, which also usually lasts 4–6 months, the shoulder becomes stiffer and stiffer even though the pain is improving. The “thawing” phase can take up to a year as the shoulder slowly regains its motion. The total duration of an idiopathic frozen shoulder is usually about 24 months; it can be much longer for patients who have trauma or an endocrinopathy.

B. Imaging

Standard AP, axillary, and lateral glenohumeral radiographs are useful to rule out glenohumeral arthritis, which can also present with limited active and passive range of motion. Imaging can also rule out calcific tendinitis, which is an acute inflammatory process in which calcifications are visible in the soft tissue. However, adhesive capsulitis is usually a clinical diagnosis, and it does not need an extensive diagnostic workup.

► Treatment

During the “acute inflammatory” and “freezing” phases, NSAIDs and physical therapy are recommended to maintain motion. There is also evidence of short-term benefit from intra-articular corticosteroid injection or oral prednisone; a meta-analysis showed that intra-articular corticosteroid injection provided better pain relief than NSAIDs in the first 8 weeks. However, no difference was seen in range of motion or pain after 12 weeks, which is similar to other noncontrolled studies. One study demonstrated improvement at 6 weeks but not 12 weeks following 30 mg of daily prednisone for 3 weeks. During the “freezing” phase, the shoulder is less painful but remains stiff. Anti-inflammatory medication is not as helpful during the “thawing” phase as it is during the “freezing” phase, and the shoulder symptoms usually resolve with time. Surgical treatments, which are rarely indicated, include manipulation under anesthesia and arthroscopic release.

► When to Refer

- When the patient does not respond after more than 6 months of conservative treatment.
- When there is no progress in or worsening of range of motion over 3 months.

Alsubheen SA et al. Effectiveness of nonsurgical interventions for managing adhesive capsulitis in patients with diabetes: a systematic review. *Arch Phys Med Rehabil*. 2019;100:350. [PMID: 30268804]

Cho CH et al. Treatment strategy for frozen shoulder. *Clin Orthop Surg*. 2019;11:249. [PMID: 31475043]

Fields BKK et al. Adhesive capsulitis: review of imaging findings, pathophysiology, clinical presentation, and treatment options. *Skeletal Radiol*. 2019;48:1171. [PMID: 30607455]

Jump CM et al. Frozen shoulder: a systematic review of cellular, molecular, and metabolic findings. *JBJS Rev*. 2021;9:e19.00153. [PMID: 33512972]

SPINE PROBLEMS

1. Low Back Pain



ESSENTIALS OF DIAGNOSIS

- Nerve root impingement is suspected when pain is leg-dominant rather than back-dominant.
- Alarming symptoms include unexplained weight loss, failure to improve with treatment, severe pain for > 6 weeks, and night or rest pain.
- Cauda equina syndrome is an emergency; often presents with bowel or bladder symptoms (or both).

► General Considerations

Low back pain remains the number one cause of disability globally and is the second most common cause for primary care visits. The annual prevalence of low back pain is 15–45%. Annual health care spending for low back and neck pain is estimated to be \$87.6 billion. Low back pain is the condition associated with the highest years lived with disability. Approximately 80% of episodes of low back pain resolve within 2 weeks and 90% resolve within 6 weeks. The exact cause of the low back pain is often difficult to diagnose; its cause is often multifactorial. There are usually degenerative changes in the lumbar spine involving the disks, facet joints, and vertebral endplates (Modic changes).

► Clinical Findings

A. Symptoms and Signs

Aggravating factors of flexion and prolonged sitting commonly suggest anterior spine disk problems, while extension pain suggests facet joint, stenosis, or sacroiliac joint problems. Alarming symptoms for back pain caused by cancer include unexplained weight loss, failure to improve with treatment, pain for more than 6 weeks, and pain at night or rest. History of cancer and age older than 50 years are other risk factors for malignancy. Alarming symptoms for infection include fever, rest pain, recent infection (urinary tract infection, cellulitis, pneumonia), or history of immunocompromise or injection drug use. The **cauda equina syndrome** is suggested by urinary retention or incontinence, saddle anesthesia, decreased anal sphincter tone or fecal incontinence, bilateral lower extremity

weakness, and progressive neurologic deficits. Risk factors for back pain due to vertebral fracture include use of corticosteroids, age over 70 years, history of osteoporosis, severe trauma, and presence of a contusion or abrasion. Back pain may also be the presenting symptom in other serious medical problems, including abdominal aortic aneurysm, peptic ulcer disease, kidney stones, or pancreatitis. The patient's previous response to treatments and the results of risk prediction tools can help guide management. The majority of patients with persistent low back pain have co-occurring areas of pain, especially axial pain (18–58%), extremity pain (6–50%), and multisite musculoskeletal pain (10–89%).

The physical examination can be conducted with the patient in the standing, sitting, supine, and finally prone positions to avoid frequent repositioning of the patient. In the standing position, the patient's posture can be observed. Commonly encountered spinal asymmetries include scoliosis, thoracic kyphosis, and lumbar hyperlordosis. The active range of motion of the lumbar spine can be assessed while standing. The common directions include flexion, extension, rotation, and lateral bending. The one-leg standing extension test assesses for pain as the patient stands on one leg while extending the spine. A positive test can be caused by pars interarticularis fractures (spondylolysis or spondylolisthesis) or facet joint arthritis.

With the patient sitting, motor strength, reflexes, and sensation can be tested (Table 41–2). The major muscles in the lower extremities are assessed for weakness by eliciting a resisted isometric contraction for about 5 seconds. Comparing the strength bilaterally to detect subtle muscle weakness is important. Similarly, sensory testing to light touch can be checked in specific dermatomes for corresponding nerve root function. Knee, ankle, and Babinski reflexes can be checked.

Table 41–2. Neurologic testing of lumbosacral nerve disorders.

Nerve Root	Motor	Reflex	Sensory Area
L1	Hip flexion	None	Groin
L2	Hip flexion	None	Thigh
L3	Extension of knee	Knee jerk	Knee
L4	Dorsiflexion of ankle	Knee jerk	Medial calf
L5	Dorsiflexion of first toe	Babinski reflex	First dorsal web space between first and second toes
S1	Plantar flexion of foot, knee flexors, or hamstrings	Ankle jerk	Lateral foot
S2	Knee flexors or hamstrings	Knee flexor	Back of the thigh
S2–S4	External anal sphincter	Anal reflex, rectal tone	Perianal area

In the supine position, the hip should be evaluated for range of motion, particularly internal rotation. The straight leg raise test puts traction and compression forces on the lower lumbar nerve roots.

In the prone position, the clinician can carefully palpate each vertebral level of the spine and sacroiliac joints for tenderness. A rectal examination is required if the cauda equina syndrome is suspected. Superficial skin tenderness to a light touch over the lumbar spine, overreaction to maneuvers in the regular back examination, low back pain on axial loading of spine in standing, and inconsistency in the straight leg raise test or on the neurologic examination suggest nonorthopedic causes for the pain or malingering.

B. Imaging

In the absence of alarming “red flag” symptoms suggesting infection, malignancy, or cauda equina syndrome, most patients do not need diagnostic imaging, including radiographs, in the first 6 weeks. The Agency for Healthcare Research and Quality guidelines for obtaining lumbar radiographs are summarized in Table 41–3. Most clinicians obtain radiographs for new back pain in patients older than 50 years. If done, radiographs of the lumbar spine should include AP and lateral views. Oblique views can be useful if the neuroforamina or bone lesions need to be visualized. MRI is the method of choice in the evaluation of symptoms not responding to conservative treatment or in the presence of red flags of serious conditions.

C. Special Tests

Electromyography or nerve conduction studies may be useful in assessing patients with possible nerve root symptoms lasting longer than 6 weeks; back pain may or may

Table 41–3. AHRQ criteria for lumbar radiographs in patients with acute low back pain.

Possible fracture
Major trauma
Minor trauma in patients > 50 years of age
Long-term corticosteroid use
Osteoporosis
> 70 years of age
Possible tumor or infection
> 50 years of age
< 20 years of age
History of cancer
Constitutional symptoms
Recent bacterial infection
Injection drug use
Immunosuppression
Supine pain
Nocturnal pain

AHRQ, Agency for Healthcare Research and Quality.

Adapted from Bigos S et al. Acute Low Back Problems in Adults. Clinical Practice Guideline Quick Reference Guide No. 14. AHCPR Publication No. 95-0643. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. December 1994.

not also be present. These tests are usually not necessary if the diagnosis of radiculopathy is clear.

► Treatment

A. Conservative

Nonpharmacologic treatments are key in the management of low back pain. Education alone improves patient satisfaction with recovery and recurrence. Patients require information and reassurance, especially when serious pathology is absent. Discussion must include reviewing safe and effective methods of symptom control as well as how to decrease the risk of recurrence with proper lifting techniques, abdominal wall/core strengthening, weight loss, and smoking cessation. Exercise, psychological therapies (eg, cognitive behavioral therapy), and multidisciplinary rehabilitation have been shown to be modestly effective for acute low back pain (strength of evidence, low). Complementary therapies, such as Tai chi, mindfulness-based stress reduction, and yoga, have shown benefit for chronic low back pain patients.

Exercise, oral NSAIDs, and serotonin and norepinephrine reuptake inhibitors (duloxetine) were shown in a systematic review to produce a clinically meaningful reduction in pain, with exercise being the only intervention that demonstrated sustained benefit after the intervention ended. Physical therapy exercise programs can be tailored to the patient's symptoms and pathology. A randomized controlled trial demonstrated that individualized physical therapy was clinically more beneficial than advice alone with sustained improvements at 6 months and 12 months. Strengthening and stabilization exercises effectively reduce pain and functional limitation compared with usual care. Heat and cold treatments have not shown any long-term benefits but may be used for symptomatic treatment. The efficacy of transcutaneous electrical nerve stimulation (TENS), back braces, and physical agents is unproven. Spinal manipulation, massage, and acupuncture have limited, low-strength evidence for chronic low back pain. Improvements in posture including chair ergonomics or standing desks, core stability strengthening, physical conditioning, and modifications of activities to decrease physical strain are keys for ongoing management. Radiofrequency denervation of facet joints, sacroiliac joints, or intervertebral disks did not result in clinically important improvement in chronic low back even when combined with a standardized exercise program in randomized controlled trials. A multidisciplinary approach to back pain care is beneficial to address the physical, psychological, and social aspects of low back pain, especially when pain is chronic, avoiding medication if possible.

If medications are needed, NSAIDs are effective in the early treatment of low back pain (see Chapter 20 and Table 5-5). Acetaminophen and oral corticosteroids are relatively ineffective for chronic low back. There is limited evidence that muscle relaxants provide short-term relief; since these medications have addictive potential, they should be used with care. Muscle relaxants are best used if there is true muscle spasm that is painful rather than simply a protective response. Opioids alleviate pain in the short term, but have the usual side effects and concerns of

long-term opioid use (Chapter 5). Treatment of more chronic neuropathic pain with alpha-2-delta ligands (eg, gabapentin), serotonin-norepinephrine reuptake inhibitors (eg, duloxetine), or tricyclic antidepressants (eg, nortriptyline) may be helpful (Chapter 5). Epidural injections may reduce pain in the short term and reduce the need for surgery in some patients within a 1-year period but not longer. Therefore, spinal injections are not recommended for initial care of patients with low back pain without radiculopathy.

B. Surgical

Indications for back surgery include cauda equina syndrome, ongoing morbidity with no response to more than 6 months of conservative treatment, cancer, infection, or severe spinal deformity. Prognosis is improved when there is an anatomic lesion that can be corrected and symptoms are neurologic. Spinal surgery has limitations. Patient selection is very important and the specific surgery recommended should have very clear indications. Patients should understand that surgery can improve their pain but is unlikely to cure it. Surgery is not generally indicated for radiographic abnormalities alone when the patient is relatively asymptomatic. Depending on the surgery performed, possible complications include persistent pain; surgical site pain, especially if bone grafting is needed; infection; neurologic damage; non-union; cutaneous nerve damage; implant failure; deep venous thrombosis; and death.

► When to Refer

- Patients with the cauda equina syndrome.
- Patients with cancer, infection, fracture, or severe spinal deformity.
- Patients who have not responded to conservative treatment.

Galliker G et al. Low back pain in the emergency department: prevalence of serious spinal pathologies and diagnostic accuracy of red flags—a systematic review. *Am J Med*. 2020;133:60. [PMID: 31278933]

Johnson SM et al. Imaging of acute low back pain. *Radiol Clin North Am*. 2019;57:397. [PMID: 30709477]

Kolber MR et al. PEER systematic review of randomized controlled trials: management of chronic low back pain in primary care. *Can Fam Physician*. 2021;67:e20. [PMID: 33483410]

Tucker HR et al. Harms and benefits of opioids for management of non-surgical acute and chronic low back pain: a systematic review. *Br J Sports Med*. 2020;54:664. [PMID: 30902816]

2. Spinal Stenosis

ESSENTIALS OF DIAGNOSIS

- Pain is usually worse with back extension and relieved by sitting.
- Occurs in older patients.
- May present with neurogenic claudication symptoms with walking.

► General Considerations

OA in the lumbar spine can cause narrowing of the spinal canal. A large disk herniation can also cause stenosis and compression of neural structures or the spinal artery resulting in “claudication” symptoms with ambulation. The condition usually affects patients aged 50 years or older.

► Clinical Findings

Patients report pain that worsens with extension. They describe reproducible single or bilateral leg symptoms that are worse after walking several minutes and that are relieved by sitting (“neurogenic claudication”). On examination, patients often exhibit limited extension of the lumbar spine, which may reproduce the symptoms radiating down the legs. A thorough neurovascular examination is recommended (Table 41–2).

► Treatment

Exercises, usually flexion-based as demonstrated by a physical therapist, can help relieve symptoms. Physical therapy showed similar results as surgical decompression in a randomized trial, though there was a 57% crossover rate from physical therapy to surgery. Facet joint corticosteroid injections can also reduce pain symptoms. While epidural corticosteroid injections have been shown to provide immediate improvements in pain and function for patients with radiculopathy, the benefits are small and only short term. Consequently, there is limited evidence to recommend epidural corticosteroids for spinal stenosis.

Surgical treatments for spinal stenosis include spinal decompression (widening the spinal canal or laminectomy), nerve root decompression (freeing a single nerve), and spinal fusion (joining the vertebra to eliminate motion and diminish pain from the arthritic joints). However, the role of surgery for spinal stenosis is limited. In one multicenter randomized trial, subgroups initially improved significantly more with surgery than with nonoperative treatment. Variables associated with greater treatment effects included lower baseline disability scores, not smoking, neuroforaminal stenosis, predominant leg pain rather than back pain, not lifting at work, and the presence of a neurologic deficit. However, long-term follow-up of the patients with symptomatic spinal stenosis who received surgery in the multicenter randomized trial showed less benefit of surgery between 4 and 8 years, suggesting that the advantage of surgery for spinal stenosis diminishes over time. A 2021 meta-analysis comparing fusion and nonfusion surgeries for lumbar spinal stenosis found no difference in clinical effects and complications, highlighting the challenge of surgical intervention for lumbar spinal stenosis.

► When to Refer

- If a patient exhibits radicular or claudication symptoms for longer than 12 weeks.
- MRI or CT confirmation of significant, symptomatic spinal stenosis.

- However, surgery has not been shown to have clear benefit over nonsurgical treatment for lumbar spinal stenosis.

Bagley C et al. Current concepts and recent advances in understanding and managing lumbar spine stenosis. F1000Res. 2019;8:137. [PMID: 30774933]

Cook CJ et al. Systematic review of diagnostic accuracy of patient history, clinical findings, and physical tests in the diagnosis of lumbar spinal stenosis. Eur Spine J. 2020;29:93. [PMID: 31312914]

Shen J et al. Comparison between fusion and non-fusion surgery for lumbar spinal stenosis: a meta-analysis. Adv Ther. 2021; 38:1404. [PMID: 33491158]

3. Lumbar Disk Herniation



ESSENTIALS OF DIAGNOSIS

- Pain with back flexion or prolonged sitting.
- Radicular pain into the leg due to compression of neural structures.
- Lower extremity numbness and weakness.

► General Considerations

Lumbar disk herniation is usually due to bending or heavy loading (eg, lifting) with the back in flexion, causing herniation or extrusion of disk contents (nucleus pulposus) into the spinal cord area. However, there may not be an inciting incident. Disk herniations usually occur from degenerative disk disease (desiccation of the annulus fibrosis) in patients between 30 and 50 years old. The L5–S1 disk is affected in 90% of cases. Compression of neural structures, such as the sciatic nerve, causes radicular pain. Severe compression of the spinal cord can cause the cauda equina syndrome, a surgical emergency.

► Clinical Findings

A. Symptoms and Signs

Discogenic pain typically is localized in the low back at the level of the affected disk and is worse with activity. “Sciatica” causes electric shock-like pain radiating down the posterior aspect of the leg often to below the knee. Symptoms usually worsen with back flexion such as bending or sitting for long periods (eg, driving). A significant disk herniation can cause numbness and weakness, including weakness of plantar flexion of the foot (L5/S1) or dorsiflexion of the toes (L4/L5). The cauda equina syndrome should be ruled out if the patient complains of perianal numbness or bowel or bladder incontinence.

B. Imaging

Plain radiographs are helpful to assess spinal alignment (scoliosis, lordosis), disk space narrowing, and OA changes. MRI is the best method to assess the level and morphology of the herniation and is recommended if surgery is planned.

► Treatment

For an acute exacerbation of pain symptoms, bed rest is appropriate for up to 48 hours. Otherwise, first-line treatments include modified activities; NSAIDs and other analgesics; and physical therapy, including core stabilization and McKenzie back exercises (<https://sportsrehab.ucsf.edu/sites/sportsrehab.ucsf.edu/files/Mckenzie%20Back%20Protocol.pdf>). The **McKenzie Method** identifies the mechanical direction of motion in the back that causes more or less pain, using careful history and physical examination to guide the treatment approach. An exercise protocol is carefully designed to centralize or alleviate the pain. Following nonsurgical treatment for a lumbar disk for over 1 year, the incidence of low back pain recurrence is at least 40% and is predicted by longer time to initial resolution of pain. In a randomized trial, oral prednisone caused a modest improvement in function at 3 weeks, but there was no significant improvement in pain in patients with acute radiculopathy who were monitored for 1 year. The initial dose for oral prednisone is approximately 1 mg/kg once daily with tapering doses over 10–15 days. Analgesics for neuropathic pain, such as the calcium channel alpha-2-delta ligands (ie, gabapentin, pregabalin) or tricyclic antidepressants, may be helpful (see Chapter 5). Epidural and transforaminal corticosteroid injections can be beneficial. A 2020 Cochrane review of 25 placebo-controlled trials provides moderate-quality evidence that epidural corticosteroid injections are effective, although the treatment effects are small (mean difference less than 10%) and short-term for improving radicular pain for individuals. There is level I evidence for the use of transforaminal injections for radicular pain from disk herniation. Additionally, epidural injections have not shown any change in long-term surgery rates for disk herniations.

The severity of pain and disability as well as failure of conservative therapy are the most important reasons for surgery. A large trial has shown that patients who underwent surgery for a lumbar disk herniation achieved greater improvement than conservatively treated patients in all primary and secondary outcomes except return to work status after 8-year follow-up. Patients with sequestered fragments, symptom duration greater than 6 months, higher levels of low back pain, or who were neither working nor disabled at baseline showed greater surgical treatment effects. Microdiscectomy is the standard method of treatment with a low rate of complications and satisfactory results in over 90% in the largest series. Minimally invasive percutaneous endoscopic spine surgery uses an endoscope to remove fragments of disk herniation (interlaminar or transforaminal approaches) under local anesthesia for the treatment of primary and recurrent disk disease. The most commonly reported complications of endoscopic lumbar surgery include dural tear, infection, and epidural hematoma. Percutaneous endoscopic discectomy has promise, though there is lack of randomized controlled trials comparing it with open microdiscectomy. Recurrent disk herniations are treated with decompression surgeries and spinal fusion surgeries. Disk replacement surgery has shown benefits in short-term pain relief, disability, and quality of life compared with spine fusion surgery.

► When to Refer

- Cauda equina syndrome.
- Progressive worsening of neurologic symptoms.
- Loss of motor function (sensory losses can be followed in the outpatient clinic).

Bailey CS et al. Surgery versus conservative care for persistent sciatica lasting 4 to 12 months. *N Engl J Med*. 2020;382:1093. [PMID: 32187469]

Butler AJ et al. Endoscopic lumbar surgery: the state of the art in 2019. *Neurospine*. 2019;16:15. [PMID: 30943703]

Carlson BB et al. Lumbar disc herniation: what has the Spine Patient Outcomes Research Trial taught us? *Int Orthop*. 2019; 43:853. [PMID: 30767043]

Oliveira CB et al. Epidural corticosteroid injections for lumbosacral radicular pain. *Cochrane Database Syst Rev*. 2020;4: CD013577. [PMID: 32271952]

4. Neck Pain



ESSENTIALS OF DIAGNOSIS

- Chronic neck pain is mostly caused by degenerative joint disease; whiplash often follows a traumatic neck injury.
- Poor posture is often a factor for persistent neck pain.

► General Considerations

Most neck pain, especially in older patients, is due to mechanical degeneration involving the cervical disks, facet joints, and ligamentous structures and may occur in the setting of degenerative changes at other sites. Pain can also come from the supporting neck musculature, which often acts to protect the underlying neck structures. Posture is a very important factor, especially in younger patients. Many work-related neck symptoms are due to poor posture and repetitive motions over time. Acute injuries can also occur secondary to trauma. Whiplash occurs from rapid flexion and extension of the neck and affects 15–40% of people in motor vehicle accidents; chronic pain develops in 5–7%. Neck fractures are serious traumatic injuries acutely and can lead to OA in the long term. Ultimately, many degenerative conditions of the neck result in cervical canal stenosis or neural foraminal stenosis, sometimes affecting underlying neural structures.

Cervical radiculopathy can cause neurologic symptoms in the upper extremities usually involving the C5–C7 disks. Patients with neck pain may report associated headaches and shoulder pain. Both peripheral nerve entrapment and cervical radiculopathy, known as a “double crush” injury, may develop. Thoracic outlet syndrome, in which there is mechanical compression of the brachial plexus and neurovascular structures with overhead positioning of the arm, should be considered in the differential diagnosis of neck pain. Other causes of neck pain include rheumatoid arthritis, fibromyalgia, osteomyelitis, neoplasms, polymyalgia

rheumatica, compression fractures, pain referred from visceral structures (eg, angina), and functional disorders. Amyotrophic lateral sclerosis, multiple sclerosis, syringomyelia, spinal cord tumors, and Parsonage-Turner syndrome can mimic myelopathy from cervical arthritis.

► Clinical Findings

A. Symptoms and Signs

Neck pain may be limited to the posterior region or, depending on the level of the symptomatic joint, may radiate segmentally to the occiput, anterior chest, shoulder girdle, arm, forearm, and hand. It may be intensified by active or passive neck motions. The general distribution of pain and paresthesias corresponds roughly to the involved dermatome in the upper extremity.

The patient's posture should be assessed, checking for shoulder rolled forward or head forward posture as well as scoliosis in the thoracolumbar spine. Patients with discogenic neck pain often complain of pain with flexion, which causes cervical disks to herniate posteriorly. Extension of the neck usually affects the neural foraminal and facet joints of the neck. Rotation and lateral flexion of the cervical spine should be measured both to the left and the right. Limitation of cervical movements is the most common objective finding.

A detailed neurovascular examination of the upper extremities should be performed, including sensory input to light touch and temperature; motor strength testing, especially the hand intrinsic muscles (thumb extension strength [C6], opponens strength [thumb to pinky] [C7], and finger abductors and adductors strength [C8–T1]); and upper extremity reflexes (biceps, triceps, brachioradialis). True cervical radiculopathy symptoms should match an expected dermatomal or myotomal distribution. The Spurling test involves asking the patient to rotate and extend the neck to one side. The clinician can apply a gentle axial load to the neck. Reproduction of the cervical radiculopathy symptoms is a positive sign of nerve root compression. Palpation of the neck is best performed with the patient in the supine position where the clinician can palpate each level of the cervical spine with the muscles of the neck relaxed.

B. Imaging and Special Tests

Radiographs of the cervical spine include the AP and lateral view of the cervical spine. The odontoid view is usually added to rule out traumatic fractures and congenital abnormalities. Oblique views of the cervical spine can provide further information about arthritis changes and assess the neural foramina for narrowing. Plain radiographs can be normal in patients who have suffered an acute cervical strain. Comparative reduction in height of the involved disk space and osteophytes are frequent findings when there are degenerative changes in the cervical spine. Loss of cervical lordosis is commonly seen but is nonspecific.

MRI is the best method to assess the cervical spine since the soft tissue structures (such as the disks, spinal cord, and nerve roots) can be evaluated. If the patient has signs of cervical radiculopathy with motor weakness, these more

sensitive imaging modalities should be obtained urgently. CT scanning is the most useful method if bony abnormalities, such as fractures, are suspected.

EMG is useful in order to differentiate peripheral nerve entrapment syndromes from cervical radiculopathy. However, sensitivity of electrodiagnostic testing for cervical radiculopathy ranges from only 50% to 71%, so a negative test does not rule out nerve root problems.

► Treatment

In the absence of trauma or evidence of infection, malignancy, neurologic findings, or systemic inflammation, the patient can be treated conservatively. More frequent observation of patients in whom very severe symptoms are present early on after an injury is recommended because high pain-related disability is a predictor of poor outcome at 1 year even if individuals decline care. Ergonomics should be assessed at work and home. A course of neck stretching, strengthening, and postural exercises in physical therapy have demonstrated benefit in relieving symptoms. A soft cervical collar can be useful for short-term use (up to 1–2 weeks) in acute neck injuries. Chiropractic manual manipulation and mobilization can provide short-term benefit for mechanical neck pain. Although the rate of complications is low (5–10/million manipulations), care should be taken whenever there are neurologic symptoms present. Specific patients may respond to use of home cervical traction. NSAIDs are commonly used and opioids may be needed in cases of severe neck pain (Tables 5–5 and 5–6). Muscle relaxants (eg, cyclobenzaprine 5–10 mg orally three times daily) can be used short term if there is muscle spasm or as a sedative to aid in sleeping. Acute radicular symptoms can be treated with neuropathic medications (eg, gabapentin 300–1200 mg orally three times daily), and a short course of oral prednisone (5–10 days) can be considered (starting at 1 mg/kg). Cervical foraminal or facet joint injections can also reduce symptoms. Surgeries are successful in reducing neurologic symptoms in 80–90% of cases, but are still considered as treatments of last resort. Common surgeries for cervical degenerative disk disease include anterior cervical discectomy with fusion and cervical disk arthroplasty. A 2020 meta-analysis of 11 randomized controlled trials showed that beyond 5 years, cervical disk arthroplasty was superior to anterior discectomy and fusion for the treatment of symptomatic cervical disk disease, with better success, less reoperation rates, and superior longevity.

► When to Refer

- Patients with severe symptoms with motor weakness.
- Surgical decompression surgery if the symptoms are severe and there is identifiable, correctable pathology.

Badhiwala JH et al. Cervical disc arthroplasty versus anterior cervical discectomy and fusion: a meta-analysis of rates of adjacent-level surgery to 7-year follow-up. *J Spine Surg.* 2020;6:217. [PMID: 32309660]

Martel JW et al. Evaluation and management of neck and back pain. *Semin Neurol.* 2019;39:41. [PMID: 30743291]

Sterling M. Best evidence rehabilitation for chronic pain part 4: neck pain. *J Clin Med.* 2019;8:E1219. [PMID: 31443149]
Strudwick K et al. Review article: best practice management of neck pain in the emergency department (part 6 of the musculoskeletal injuries rapid review series). *Emerg Med Australas.* 2018;30:754. [PMID: 30168261]

UPPER EXTREMITY

1. Lateral & Medial Epicondylitis (Tendinopathy)



ESSENTIALS OF DIAGNOSIS

- ▶ Tenderness over the lateral or medial epicondyle.
- ▶ Diagnosis of tendinopathy is confirmed by pain with resisted strength testing and passive stretching of the affected tendon and muscle unit.
- ▶ Physical therapy and activity modification are more successful than anti-inflammatory treatments.

► General Considerations

Tendinopathies involving the wrist extensors, flexors, and pronators are very common complaints. The underlying mechanism is chronic repetitive overuse causing micro-trauma at the tendon insertion, although acute injuries can occur as well if the tendon is strained due to excessive loading. The traditional term “epicondylitis” is a misnomer because histologically tendinosis or degeneration in the tendon is seen rather than acute inflammation. Therefore, these entities should be referred to as “tendinopathy” or “tendinosis.” Lateral epicondylitis involves the wrist extensors, especially the extensor carpi radialis brevis. This is usually caused by lifting with the wrist and the elbow extended. Medial epicondylitis involves the wrist flexors and most commonly the pronator teres tendon. Ulnar neuropathy and cervical radiculopathy should be considered in the differential diagnosis.

► Clinical Findings

A. Symptoms and Signs

For lateral epicondylitis, the patient describes pain with the arm and wrist extended. For example, common complaints include pain while shaking hands, lifting objects, using a computer mouse, or hitting a backhand in tennis (“tennis elbow”). Medial epicondylitis presents with pain during motions in which the arm is repetitively pronated or the wrist is flexed. This is also known as “golfer’s elbow” due to the motion of turning the hands over during the golf swing. For either, tenderness directly over the epicondyle is present, especially over the posterior aspect where the tendon insertion occurs. The proximal tendon and musculotendinous junction can also be sore. To confirm that the pain is due to tendinopathy, pain can be reproduced over the epicondyle with resisted wrist extension and third digit

extension for lateral epicondylitis and resisted wrist pronation and wrist flexion for medial epicondylitis. The pain is also often reproduced with passive stretching of the affected muscle groups, which can be performed with the arm in extension. It is useful to check the ulnar nerve (located in a groove at the posteromedial elbow) for tenderness as well as to perform a Spurling test for cervical radiculopathy.

B. Imaging

Radiographs are often normal, although a small traction spur may be present in chronic cases (enthesopathy). Diagnostic investigations are usually unnecessary, unless the patient does not improve after up to 3 months of conservative treatment. At that point, a patient who demonstrates significant disability due to the pain should be assessed with an MRI or ultrasound. Ultrasound and MRI can visualize the tendon and confirm tendinosis or tears.

► Treatment

Treatment is usually conservative, including patient education regarding activity modification and management of symptoms. Ice and NSAIDs can help with pain (Table 5–5). The mainstay of treatment is physical therapy exercises. The most important steps are to begin a good stretching program followed by strengthening exercises, particularly eccentric ones. Counterforce elbow braces might provide some symptomatic relief, although there is no published evidence to support their use. If the patient has severe or long-standing symptoms, injections can be considered. A randomized trial showed improvement with corticosteroid injection at 1 month as well as evidence of decreased tendon thickness and Doppler changes but no improvement at 3 months. Percutaneous needle tenotomy showed some positive results as an alternative to surgery but lacks demonstrated efficacy in a randomized control study. Evidence suggests that PRP and autologous blood injections both have positive benefits in lateral epicondylitis. In a randomized controlled trial comparing PRP injection to controls ($n = 119$), the PRP-treated patients reported 55.1% improvement in their pain scores at 12 weeks compared to 47.4% in the control patients ($P = 0.163$). More significant improvement was seen at 24 weeks; 71.5% improvement in the pain scores in the PRP-treated patients compared to 56.1% in the control patients ($P = 0.019$). (A 25% improvement of pain symptoms was considered to be clinically significant.) However, the varied methods of PRP preparations and varied post-injection recommendations for rest and physiotherapy make interpretation of various study results difficult to summarize. Compared to ultrasound therapy, extracorporeal shock wave therapy has shown better efficacy for pain relief (as measured with visual analog scales) and better grip strength. However, it is used less commonly than injection treatments and is still considered second-line therapy.

► When to Refer

Patients not responding to 6 months of conservative treatment should be referred for an injection procedure (PRP or tenotomy), surgical debridement, or repair of the tendon.

- Houck DA et al. Treatment of lateral epicondylitis with autologous blood, platelet-rich plasma, or corticosteroid injections: a systematic review of overlapping meta-analyses. *Orthop J Sports Med.* 2019;7:2325967119831052. [PMID: 30899764]
- Kim GM et al. Current trends for treating lateral epicondylitis. *Clin Shoulder Elb.* 2019;22:227. [PMID: 33330224]
- Shergill R et al. Ultrasound-guided interventions in lateral epicondylitis. *J Clin Rheumatol.* 2019;25:e27. [PMID: 30074911]
- Yan C et al. A comparative study of the efficacy of ultrasomics and extracorporeal shock wave in the treatment of tennis elbow: a meta-analysis of randomized controlled trials. *J Orthop Surg Res.* 2019;14:248. [PMID: 31387611]

2. Carpal Tunnel Syndrome

ESSENTIALS OF DIAGNOSIS

- ▶ Pain, burning, and tingling in the distribution of the median nerve.
- ▶ Initially, most bothersome during sleep.
- ▶ Late weakness or atrophy of the thenar eminence.
- ▶ Can be caused by repetitive wrist activities.
- ▶ Commonly seen during pregnancy and in patients with diabetes mellitus or rheumatoid arthritis.

► General Considerations

An entrapment neuropathy, carpal tunnel syndrome is a painful disorder caused by compression of the median nerve between the carpal ligament and other structures within the carpal tunnel. The contents of the tunnel can be compressed by synovitis of the tendon sheaths or carpal joints, recent or malhealed fractures, tumors, tissue infiltration, and occasionally congenital syndromes (eg, mucopolysaccharidoses). The disorder may occur in fluid retention of pregnancy, in individuals with a history of repetitive use of the hands, or following injuries of the wrists. Carpal tunnel syndrome can also be a feature of many systemic diseases, such as rheumatoid arthritis and other rheumatic disorders (inflammatory tenosynovitis), myxedema, amyloidosis, sarcoidosis, leukemia, acromegaly, and hyperparathyroidism. There is a familial type of carpal tunnel syndrome; the etiologic factor is unknown.

► Clinical Findings

A. Symptoms and Signs

The initial symptoms are pain, burning, and tingling in the distribution of the median nerve (the palmar surfaces of the thumb, the index and long fingers, and the radial half of the ring finger). Aching pain may radiate proximally into the forearm and occasionally proximally to the shoulder and over the neck and chest. Pain is exacerbated by manual activity, particularly by extremes of volar flexion or dorsiflexion of the wrist. It is most bothersome at night. Impairment of sensation in the median nerve distribution may or may not be demonstrable. Subtle disparity between

the affected and opposite sides can be shown by testing for two-point discrimination or by requiring the patient to identify different textures of cloth by rubbing them between the tips of the thumb and the index finger. A **Tinel sign** may be positive. A **Tinel sign** is tingling or shock-like pain on volar wrist percussion. The **Phalen sign** is pain or paresthesia in the distribution of the median nerve when the patient flexes both wrists to 90 degrees for 60 seconds. The **carpal compression test**, in which numbness and tingling are induced by the direct application of pressure over the carpal tunnel, may be more sensitive and specific than the Tinel and Phalen tests. Muscle weakness or atrophy, especially of the thenar eminence, can appear later than sensory disturbances as compression of the nerve worsens.

B. Imaging

Ultrasound can demonstrate flattening of the median nerve beneath the flexor retinaculum. Sensitivity of ultrasound for carpal tunnel syndrome is variable but estimated between 54% and 98%.

C. Special Tests

Electromyography and nerve conduction studies show evidence of sensory conduction delay before motor delay, which can occur in severe cases. Electrodiagnosis can provide information on focal median mononeuropathy at the wrist and can classify carpal tunnel syndrome from mild to severe.

► Treatment

Treatment is directed toward relief of pressure on the median nerve. When a causative lesion is discovered, it should be treated appropriately. Otherwise, patients in whom carpal tunnel syndrome is suspected should modify their hand activities. The affected wrist can be splinted in the neutral position for up to 3 months, but a series of Cochrane reviews show limited evidence for splinting, exercises, and ergonomic positioning. Moderate evidence supported benefit from several physical therapy and electrophysical modalities (eg, ultrasound therapy and radial extracorporeal shockwave therapy). These modalities provided short-term and mid-term relief of carpal tunnel syndrome symptoms in different studies. Oral corticosteroids or NSAIDs have also shown benefit for carpal tunnel syndrome. Methylprednisolone injections were found to have more effect at 10 weeks than placebo, but the benefits diminished by 1 year.

Compared to trigger finger management, which usually includes injections, as many as 71% of patients with carpal tunnel directly undergo surgery without first getting injections. There is strong evidence that a steroid injection to the carpal tunnel is more effective in the short term than surgery. Knowledge of pertinent anatomy and consistent technique are important to ensuring accurate needle placement during carpal tunnel injection; the accuracy of injection was only 76% in a 2020 study, lower than previously reported. A randomized, controlled trial showed both corticosteroid injection and surgery resolved symptoms but only decompressive surgery led to resolution of

neurophysiologic changes. Carpal tunnel release surgery can be beneficial if the patient has a positive electrodiagnostic test, at least moderate symptoms, high clinical probability, unsuccessful nonoperative treatment, and symptoms lasting longer than 12 months. Surgery can be done with an open approach or endoscopically, both yielding similar good improvements.

► When to Refer

- If symptoms persist more than 3 months despite conservative treatment, including the use of a wrist splint.
- If thenar muscle (eg, abductor pollicis brevis) weakness or atrophy develops.

Green DP et al. Accuracy of carpal tunnel injection: a prospective evaluation of 756 patients. *Hand (N Y)*. 2020;15:54. [PMID: 30003816]

Huisstede BM et al. Carpal tunnel syndrome: effectiveness of physical therapy and electrophysical modalities. An updated systematic review of randomized controlled trials. *Arch Phys Med Rehabil*. 2018;99:1623. [PMID: 28942118]

Huisstede BM et al. Effectiveness of surgical and postsurgical interventions for carpal tunnel syndrome—a systematic review. *Arch Phys Med Rehabil*. 2018;99:1660. [PMID: 28577858]

Urits I et al. Recent advances in the understanding and management of carpal tunnel syndrome: a comprehensive review. *Curr Pain Headache Rep*. 2019;23:70. [PMID: 31372847]

3. Dupuytren Contracture



- Benign fibrosing disorder of the palmar fascia.
- Contracture of one or more fingers can lead to limited hand function.

► General Considerations

This relatively common disorder is characterized by hyperplasia of the palmar fascia and related structures, with nodule formation and contracture of the palmar fascia. The cause is unknown, but the condition has a genetic predisposition and occurs primarily in White men over 50 years of age, particularly in those of Celtic descent. The incidence is higher among patients with alcohol use disorder and those with chronic systemic disorders (especially cirrhosis). It is also associated with systemic fibrosing syndrome, which includes plantar fibromatosis (10% of patients), Peyronie disease (1–2%), mediastinal and retroperitoneal fibrosis, and Riedel struma. The onset may be acute, but slowly progressive chronic disease is more common.

► Clinical Findings

Dupuytren contracture manifests itself by nodular or cord-like thickening of one or both hands, with the fourth and fifth fingers most commonly affected. The patient

may complain of tightness of the involved digits, with inability to satisfactorily extend the fingers, and on occasion there is tenderness. The resulting cosmetic problems may be unappealing, but in general the contracture is well tolerated since it exaggerates the normal position of function of the hand.

► Treatment

Corticosteroid injections, percutaneous needle aponeurotomy, collagenase *Clostridium histolyticum* injections, and open fasciectomy are common treatment options. If the palmar nodule is growing rapidly, injections of triamcinolone or collagenase into the nodule may be of benefit, while the injection of collagenase *C histolyticum* lyses collagen, thereby disrupting the contracted cords. Surgical options include open fasciectomy, partial fasciectomy, or percutaneous needle aponeurotomy and are indicated in patients with more severe flexion contractures. Splinting after surgery is beneficial. Recurrence and more adverse events are more likely to occur after surgery than with nonoperative treatments. Overall, treatment success is lower for PIP joints than for MCP joints. Fasciectomies are more successful for severe conditions involving multiple fingers, while percutaneous needle aponeurotomy is cost-effective and useful for milder cases and for single digit involvement. *C histolyticum* injections are not currently cost effective due to high reintervention rates, regardless of severity. Compared to placebo, tamoxifen therapy produced moderate evidence of improvement before or after a fasciectomy.

► When to Refer

Referral can be considered when one or more digits are affected by severe contractures, which interfere with everyday activities and result in functional limitations.

Leafblad ND et al. Outcomes and direct costs of needle aponeurotomy, collagenase injection, and fasciectomy in the treatment of Dupuytren contracture. *J Hand Surg Am*. 2019;44:919. [PMID: 31537401]

Soreide E et al. Treatment of Dupuytren's contracture: a systematic review. *Bone Joint J*. 2018;100-B:1138. [PMID: 30168768]

Yoon AP et al. Cost-effectiveness of recurrent Dupuytren contracture treatment. *JAMA Netw Open*. 2020;3:e2019861. [PMID: 33030553]

4. Bursitis



- Often occurs around bony prominences where it is important to reduce friction.
- Typically presents with local swelling that is painful acutely.
- Septic bursitis can present without fever or systemic signs.



Figure 41–1. Chronic aseptic olecranon bursitis without erythema or tenderness. (Used, with permission, from Richard P. Usatine, MD, in Usatine RP, Smith MA, Mayeaux EJ Jr, Chumley HS. *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. McGraw-Hill, 2019.)

► General Considerations

Inflammation of bursae—the synovium-like cellular membranes overlying bony prominences—may be secondary to trauma, infection, or arthritic conditions such as gout, rheumatoid arthritis, or OA. Bursitis can result from infection. The two common sites are the olecranon (Figure 41–1) and prepatellar bursae; however, others include subdeltoid, ischial, trochanteric, and semimembranosus-gastrocnemius (Baker cyst) bursae. The bursitis can be septic. Aseptic bursitis is usually afebrile.

► Clinical Findings

A. Symptoms and Signs

Bursitis presents with focal tenderness and swelling and is less likely to affect range of motion of the adjacent joint. Olecranon or prepatellar bursitis, for example, causes an oval (or, if chronic, bulbous) swelling at the tip of the elbow or knee and does not affect joint motion. Tenderness, erythema and warmth, cellulitis, a report of trauma, and evidence of a skin lesion are more common in septic bursitis but can be present in aseptic bursitis as well. Patients with septic bursitis can be febrile but the absence of fever does not exclude infection; one-third of those with septic olecranon bursitis are afebrile.

A bursa can also become symptomatic when it ruptures. This is particularly true for Baker cyst, the rupture of which can cause calf pain and swelling that mimic thrombophlebitis.

B. Imaging

Imaging is unnecessary unless there is concern for osteomyelitis, trauma, or other underlying pathology. Ruptured Baker cysts are imaged easily by sonography or MRI; imaging a presumed Baker cyst can exclude a deep venous thrombosis, which can be mimicked by a ruptured Baker cyst.

C. Special Tests

Acute swelling and redness at a bursal site call for aspiration to rule out infection especially if the patient is either febrile (temperature more than 37.8°C) or has prebursal warmth (temperature difference greater than 2.2°C) or both. A bursal fluid white blood cell count of greater than 1000/mcL ($1 \times 10^9/L$) indicates inflammation from infection, rheumatoid arthritis, or gout. The bursal fluid of septic bursitis characteristically contains a purulent aspirate, fluid-to-serum glucose ratio less than 50%, white blood cell count more than 3000 cells/mcL ($3 \times 10^9/L$), polymorphonuclear cells more than 50%, and a positive Gram stain for bacteria. Most cases are caused by *Staphylococcus aureus*; the Gram stain is positive in two-thirds.

► Treatment

In general, aspiration and corticosteroid injections in mild, nonseptic bursitis should be avoided to reduce complications of iatrogenic infection and skin atrophy. Bursitis caused by trauma responds to local heat, rest, NSAIDs (Table 5–5), and local corticosteroid injections. Repetitive minor trauma to the olecranon bursa should be eliminated by avoiding resting the elbow on a hard surface or by wearing an elbow pad. For chronic aseptic bursitis or when there are athletic or occupational demands, aspiration with intrabursal steroid injection can be performed. Ultrasound-guided aspiration and injection can improve the accuracy of the procedures. Treatment of a ruptured Baker cyst includes rest, leg elevation, and possibly injection of triamcinolone, 20–40 mg into the knee anteriorly (the knee compartment communicates with the cyst).

Treatment for septic bursitis involves incision and drainage and antibiotics usually delivered intravenously, especially against *S aureus*.

► When to Refer

- Surgical removal of the bursa is indicated only for cases in which infections occur.
- Elective surgical removal can be considered for persistent symptoms affecting activities of daily living.

HIP

1. Hip Fractures



ESSENTIALS OF DIAGNOSIS

- ▶ Internal rotation of the hip is the best provocative diagnostic maneuver.
- ▶ Hip fractures should be surgically repaired as soon as possible (within 24 hours).
- ▶ Delayed treatment of hip fractures in older adults leads to increased complications and mortality.

► General Considerations

Approximately 4% of the 7.9 million fractures that occur each year in the United States are hip fractures. There is a high mortality rate among older adult patients following hip fracture, with death occurring in 8–9% within 30 days and in approximately 25–30% within 1 year. Osteoporosis, female sex, height greater than 5-feet 8-inches, and age over 50 years are risk factors for hip fracture. Hip fractures usually occur after a fall. High-velocity trauma is needed in younger patients. Stress fractures can occur in athletes or individuals with poor bone mineral density following repetitive loading activities.

► Clinical Findings

A. Symptoms and Signs

Patients typically report pain in the groin, though pain radiating to the lateral hip, buttock, or knee can also commonly occur. If a displaced fracture is present, the patient will not be able to bear weight and the leg may be externally rotated. Gentle logrolling of the leg with the patient supine helps rule out a fracture. Examination of the hip demonstrates pain with deep palpation in the area of the femoral triangle (similar to palpating the femoral artery). Provided the patient can tolerate it, the clinician can, with the patient supine, flex the hip to 90 degrees with the knee flexed to 90 degrees. The leg can then be internally and externally rotated to assess the range of motion on both sides. Pain with internal rotation of the hip is the most sensitive test to identify intra-articular hip pathology. Hip flexion, extension, abduction, and adduction strength can be tested.

Patients with hip stress fractures have less pain on physical examination than described previously but typically have pain with weight bearing. The Trendelenburg test can be performed to examine for weakness or instability of the hip abductors, primarily the gluteus medius muscle; the patient balances first on one leg, raising the non-standing knee toward the chest. The clinician can stand behind the patient and observe for dropping of the pelvis and buttock on the non-stance side. Another functional test is asking the patient to hop or jump during the examination. If the patient has a compatible clinical history of pain and is unable or unwilling to hop, then a stress

fracture should be ruled out. The back should be carefully examined in patients with hip complaints, including examining for signs of sciatica.

Following displaced hip fractures, delay of operative intervention leads to an increased risk of perioperative morbidity and mortality. A thorough medical evaluation and treatment should be done to maximize the patient's ability to undergo operative intervention. A patient who was unable to get up after a fall may have been immobile for hours or even days. Her clinician must exclude rhabdomyolysis, hypothermia, deep venous thrombosis, pulmonary embolism, and other possible sequelae of prolonged immobilization.

B. Imaging

Useful radiographic imaging of the hip includes AP views of the pelvis and bilateral hips and frog-leg-lateral views of the painful hip. A CT scan or MRI may be necessary to identify the hip fracture pattern or to exclude non-displaced fractures. Hip fractures are generally described by location, including femoral neck, intertrochanteric, or subtrochanteric.

► Treatment

Almost all patients with a hip fracture will require surgery and may need to be admitted to the hospital for pain control while they await surgery. Surgery is recommended within the first 24 hours because studies have shown that delaying surgery 48 hours results in at least twice the rate of major and minor medical complications, including pneumonia, pressure injuries (formerly pressure ulcers), and deep venous thrombosis. High-volume centers have multidisciplinary teams (including orthopedic surgeons, internists, social workers, and specialized physical therapists) to comanage these patients, which improves perioperative medical care and expedites preoperative evaluation leading to reduced costs. During the months of hip fracture recovery, prevention of pneumonia and functional decline and treatment of cardiac disease can reduce mortality.

Stress fractures in active patients require a period of protected weight bearing and a gradual return to activities, although it may take 4–6 months before a return to normal activities. Femoral neck fractures are commonly treated with hemiarthroplasty or total hip replacement. This allows the patient to begin weight bearing immediately postoperatively. Peritrochanteric hip fractures are treated with open reduction internal fixation, where plate and screw construct or intramedullary devices are used. The choice of implant will depend on the fracture pattern. Since fracture fixation requires the fracture to proceed to union, the patient may need to have protected weight bearing during the early postoperative period. Dislocation, periprosthetic fracture, and avascular necrosis of the hip are common complications after surgery. Patients should be mobilized as soon as possible postoperatively to avoid pulmonary complications and pressure injuries. Supervised physical therapy and rehabilitation are important for the patient to regain as much function as possible. Unfortunately, most patients following hip fractures will lose some

degree of independence. Patients with hip fracture surgery when compared with elective total hip replacement have been shown to have higher risk of in-hospital mortality.

► Prevention

Bone density screening can identify patients at risk for osteopenia or osteoporosis, and treatment can be planned accordingly (see Chapter 26). There is strong evidence that bisphosphonates, denosumab, and teriparatide reduce fractures compared with placebo, with relative risk reductions of 0.60–0.80 for nonvertebral fractures. There is an increase in atypical femoral fractures with bisphosphonate use (relative risk 1.7), especially in patients of an Asian race in North America, patients with femoral bowing, and patients who had used glucocorticoids. Consensus is that there is benefit in using bisphosphonates, particularly during the third through fifth years of therapy, with considerations for drug holidays. After 5 years of bisphosphonate use, there is an increased risk for atypical femur fractures. Nutrition and bone health (bone densitometry, serum calcium and 25-OH vitamin D levels) should be reviewed with the patient. However, there is no evidence that increasing calcium intake prevents hip fractures. For patients with decreased mobility, systemic anticoagulation should be considered to avoid deep venous thrombosis (see Table 14–14). Fall prevention exercise programs are available for older adult patients at risk for falls and hip fractures. Hip protectors are uncomfortable and have less use in preventing fractures.

► When to Refer

- All patients in whom hip fracture is suspected.
- All patients with hip fracture or in whom the diagnosis is uncertain after radiographs.

Barceló M et al. Hip fracture and mortality: study of specific causes of death and risk factors. *Arch Osteoporos*. 2021;16:15. [PMID: 33452949]

Black DM et al. Atypical femur fracture risk versus fragility fracture prevention with bisphosphonates. *N Engl J Med*. 2020;383:743. [PMID: 32813950]

Guyen O. Hemiarthroplasty or total hip arthroplasty in recent femoral neck fractures? *Orthop Traumatol Surg Res*. 2019;105:S95. [PMID: 30449680]

Sobolev B et al; Canadian Collaborative Study of Hip Fractures. Mortality effects of timing alternatives for hip fracture surgery. *CMAJ*. 2018;190:E923. [PMID: 30087128]

Stirton JB et al. Total hip arthroplasty for the management of hip fracture: a review of the literature. *J Orthop*. 2019;16:141. [PMID: 30886461]

2. Hip Osteoarthritis



ESSENTIALS OF DIAGNOSIS

- Pain deep in the groin on the affected side.
- Swelling.
- Degeneration of joint cartilage.
- Loss of active and passive range of motion in severe OA.

► General Considerations

In the United States, the prevalence of OA will grow as the number of persons over age 65 years doubles to more than 70 million by 2030. Cartilage loss and OA symptoms are preceded by damage to the collagen-proteoglycan matrix. The etiology of OA is often multifactorial, including previous trauma, prior high-impact activities, genetic factors, obesity, and rheumatologic or metabolic conditions. Femoroacetabular impingement, which affects younger active patients, is considered an early development of hip OA.

► Clinical Findings

A. Symptoms and Signs

OA usually causes pain in the affected joint with loading of the joint or at the extremes of motion. Mechanical symptoms—such as swelling, grinding, catching, and locking—suggest internal derangement, which is indicated by damaged cartilage or bone fragments that affect the smooth range of motion expected at an articular joint. Pain can also produce the sensation of “buckling” or “giving way” due to muscle inhibition. As the joint degeneration becomes more advanced, the patient loses active range of motion and may lose passive range of motion as well.

Patients complain of pain deep in the groin on the affected side and have problems with weight-bearing activities such as walking, climbing stairs, and getting up from a chair. They may limp and develop a lurch during their gait, leaning toward the unaffected side as they walk to reduce pressure on the arthritic hip. The most specific findings to identify hip osteoarthritis were squat causing posterior pain, groin pain on passive abduction or adduction, abductor weakness, and decreased passive hip adduction or less passive internal rotation compared with the contralateral leg. The presence of normal passive hip adduction was most useful for suggesting the absence of OA (LR-, 0.25 [95% CI, 0.11–0.54]).

B. Imaging

An anterior-posterior weight-bearing radiograph of the pelvis with a lateral view of the symptomatic hip are preferred views for evaluation of hip OA. Joint space narrowing and sclerosis suggest early OA. Findings of femoroacetabular impingement are commonly reported on radiograph reports with arthritic changes and anatomic variations involving the acetabulum and femoral head neck junction. After age 35, MRI of the hips already show labral changes in almost 70% of asymptomatic patients. Osteophytes near the femoral head or acetabulum and subchondral bone cysts (advanced Kellgren and Lawrence grade), superior or (supero) lateral femoral head migration, and subchondral sclerosis suggest the patient will more likely progress to total hip replacement. However, not all patients with radiographic hip OA have hip or groin pain; the converse is also true.

► Treatment

A. Conservative

Changes in the articular cartilage are irreversible. Therefore, a cure for the diseased joint is not possible, although

symptoms or structural issues can be managed to try to maintain activity level. Conservative treatment for patients with OA includes activity modification, proper footwear, therapeutic exercises, weight loss, and use of assistive devices (such as a cane). A 2014 randomized study found that physical therapy did not lead to greater improvement in pain or function compared with sham treatment in patients with hip OA. Analgesics may be effective in some cases. Corticosteroid injections can be considered for short-term relief of pain; however, hip injections are best performed under fluoroscopic, ultrasound, or CT guidance to ensure accurate injection in the joint.

B. Surgical

Joint replacement surgeries are effective and cost-effective for patients with significant symptoms and functional limitations, providing improvements in pain, function, and quality of life. Various surgical techniques and computer-assisted navigation during operation continue to be investigated. A review of nine randomized controlled trials concluded that a direct anterior approach for hip replacement was associated with a shorter incision, lower blood loss, lower pain scores, and earlier functional recovery. However, there was no significant difference in complication rates between groups for the direct anterior or posterior approaches nor were there any differences in patient-reported postoperative outcome measures at 1 year or beyond. There has not been clear clinical benefit of minimally invasive surgery compared to the standard invasive surgery, except for less total blood loss, shorter duration of surgery, and a shorter length of hospital stay.

Hip resurfacing surgery is an alternative for younger patients. Rather than use a traditional artificial joint implant of the whole neck and femur, only the femoral head is removed and replaced. Evidence to date suggests that hip resurfacing is comparable to total hip replacement. The cumulative survival rate of this implant at 10 years is estimated to be 94%. Concerns following resurfacing surgery include the risk of femoral neck fracture and collapse of the head. In a systematic review of national databases, the average time to revision was 3.0 years for metal-on-metal hip resurfacing versus 7.8 years for total hip arthroplasty. Dislocations were more frequent with total hip arthroplasty than metal-on-metal hip resurfacing: 4.4 vs 0.9 per 1000 person-years, respectively.

Guidelines recommend prophylaxis for venous thromboembolic disease for a minimum of 14 days after arthroplasty of the hip or knee using warfarin, low-molecular-weight heparin, fondaparinux, aspirin, rivaroxaban, dabigatran, apixaban, or portable mechanical compression (see Table 14–14). While bleeding risks are similar, patients taking warfarin are more likely to experience DVT and PE than patients taking rivaroxaban (see Chapter 14).

► When to Refer

Patients with sufficient disability, limited benefit from conservative therapy, and evidence of severe OA on imaging can be referred for joint replacement surgery.

Hunter DJ et al. Osteoarthritis. Lancet. 2019;393:1745. [PMID: 31034380]

Metcalfe D et al. Does this patient have hip osteoarthritis? The Rational Clinical Examination Systematic Review. JAMA. 2019;322:2323. [PMID: 31846019]

Sauder N et al. The AAHKS Clinical Research Award: no evidence for superior patient-reported outcome scores after total hip arthroplasty with the direct anterior approach at 1.5 months postoperatively, and through a 5-year follow-up. J Arthroplasty. 2020;35:S15. [PMID: 32169382]

Teirlinck CH et al. Prognostic factors for progression of osteoarthritis of the hip: a systematic review. Arthritis Res Ther. 2019; 21:192. [PMID: 31443685]

KNEE

1. Knee Pain



ESSENTIALS OF DIAGNOSIS

- ▶ Effusion can occur with intra-articular pathology (eg, OA, meniscus and cruciate ligament tears).
- ▶ Acute knee swelling (due to hemarthrosis) within 2 hours may indicate ligament injuries or patellar dislocation or fracture.

► General Considerations

The knee is the largest joint in the body and is susceptible to injury from trauma, inflammation, infection, and degenerative changes. Table 41–4 shows the differential diagnosis of knee pain. OA of the knees is common after 50 years of age and can develop due to previous trauma, aging, activities, alignment issues, and genetic predisposition.

► Clinical Findings

A. Symptoms and Signs

Evaluation of knee pain should begin with questions regarding duration and rapidity of symptom onset and the

Table 41–4. Differential diagnosis of knee pain.

Mechanical dysfunction or disruption

Internal derangement of the knee: injury to the menisci or ligaments

Degenerative changes caused by osteoarthritis

Dynamic dysfunction or misalignment of the patella

Fracture as a result of trauma

Intra-articular inflammation or increased pressure

Internal derangement of the knee: injury to the menisci or ligaments

Inflammation or infection of the knee joint

Ruptured popliteal (Baker) cyst

Peri-articular inflammation

Internal derangement of the knee: injury to the menisci or ligaments

Prepatellar or anserine bursitis

Ligamentous sprain

mechanism of injury or aggravating symptoms. Overuse or degenerative problems can occur with stress or compression from sports, hobbies, or occupation. A history of trauma or previous orthopedic problems with, or surgery to, the affected knee should also be specifically queried. Symptoms of infection (fever, recent bacterial infections, risk factors for sexually transmitted infections [such as gonorrhea] or other bacterial infections [such as staphylococcal infection]) should always be elicited.

Common symptom complaints include the following:

1. Grinding, clicking, or popping with bending may be indicative of OA or the patellofemoral syndrome.
2. “Locking” or “catching” when walking suggests an internal derangement, such as meniscal injury or a loose body in the knee.
3. Intra-articular swelling of the knee or an effusion indicates an internal derangement or a synovial pathology. Large swelling may cause a popliteal (Baker) cyst. Acute swelling within minutes to hours suggests a hemarthrosis, most likely due to an anterior cruciate ligament (ACL) injury, fracture, or patellar dislocation, especially if trauma is involved.
4. Lateral “snapping” with flexion and extension of the knee may indicate inflammation of the iliotibial band.
5. Pain that is worsened with bending and walking downstairs suggests issues with the patellofemoral joint, usually degenerative such as chondromalacia of the patella or OA.
6. Pain that occurs when rising after prolonged sitting suggests a problem with tracking of the patella.

When there is a knee joint effusion, physical examination will demonstrate swelling in the hollow or dimple around the patella and distention of the suprapatellar space.

The location of the knee pain combined with specific tests for anatomic structures are frequently sufficient to establish a diagnosis (Tables 41–5 and 41–6).

B. Laboratory Findings

Laboratory testing of aspirated joint fluid, when indicated, can lead to a definitive diagnosis in most patients (see Tables 20–2 and 20–3).

C. Imaging

Knee pain is evaluated with plain (weight-bearing) radiographs and MRI most commonly, but CT and ultrasound are sometimes useful.

An acute hemarthrosis represents bloody swelling that usually occurs within the first 1–2 hours following trauma. In situations where the trauma may be activity-related and not a result of a fall or collision, the differential diagnosis most commonly includes ACL tear (responsible for more than 70% in adults), fracture (patella, tibial plateau, femoral supracondylar, growth plate [physeal]), and patellar dislocation. Meniscal tears are unlikely to cause large hemarthrosis.

Table 41–5. Location of common causes of knee pain.

Medial knee pain

- Medial compartment osteoarthritis
- Medial collateral ligament strain
- Medial meniscal injury
- Anserine bursitis (pain over the proximal medial tibial plateau)

Anterior knee pain

- Patellofemoral syndrome (often bilateral)
- Osteoarthritis
- Prepatellar bursitis (associated with swelling anterior to the patella)
- “Jumper’s knee” (pain at the inferior pole of the patella)
- Septic arthritis
- Gout or other inflammatory disorder

Lateral knee pain

- Lateral meniscal injury
- Iliotibial band syndrome (pain superficially along the distal iliotibial band near lateral femoral condyle or lateral tibial insertion)
- Lateral collateral ligament sprain (rare)

Posterior knee pain

- Popliteal (Baker) cyst
- Osteoarthritis
- Meniscal tears
- Hamstring or calf tendinopathy

Bunt CW et al. Knee pain in adults and adolescents: the initial evaluation. Am Fam Physician. 2018;98:576. [PMID: 30325638]

2. Anterior Cruciate Ligament Injury



ESSENTIALS OF DIAGNOSIS

- An injury involving an audible pop when the knee buckles.
- Acute swelling immediately (or within 2 hours).
- Instability occurs with lateral movement activities and going down stairs.

► General Considerations

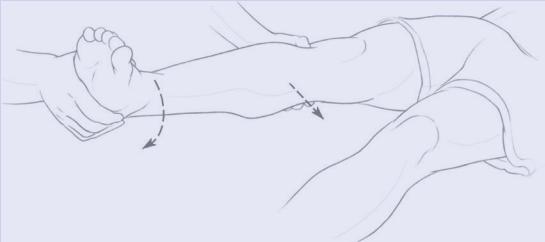
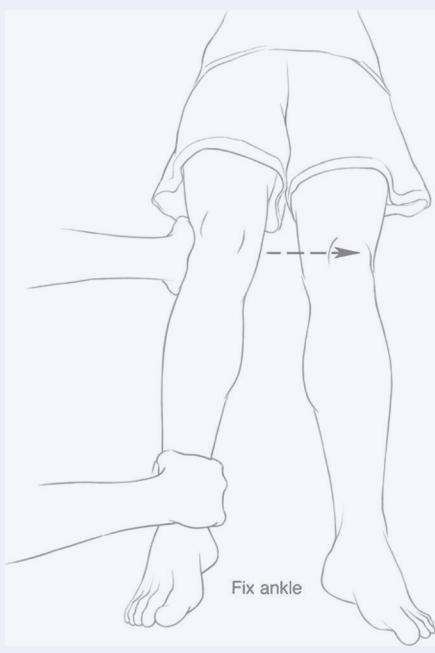
The ACL connects the posterior aspect of the lateral femoral condyle to the anterior aspect of the tibia. Its main function is to control anterior translation of the tibia on the femur. It also provides rotational stability of the tibia on the femur. ACL tears are common with sporting injuries. They can result from both contact (valgus blow to the knee) and non-contact (jumping, pivoting, and deceleration) activities. The patient usually falls down following the injury, has acute swelling and difficulty with weight bearing, and complains of instability. ACL injuries are common in skiing, soccer, football, and basketball among young adolescents and middle-aged patients. Prepubertal and older patients usually sustain fractures instead of ligamentous injuries.

Table 41–6. Knee examination.

Maneuver	Description
Inspection	Examine for the alignment of the lower extremities (varus, valgus, knee recurvatum), ankle eversion and foot pronation, gait, "SEADS" (swelling, erythema, atrophy, deformity, surgical scars).
Palpation	Include important landmarks: patellofemoral joint, medial and lateral joint lines (especially posterior aspects), pes anserine bursa, distal iliotibial band and Gerdy tubercle (iliotibial band insertion).
Range of motion testing 	Check range of motion actively (patient performs) and passively (clinician performs), especially with flexion and extension of the knee normally 0–10 degrees of extension and 120–150 degrees of flexion.
Knee strength testing	Test resisted knee extension and knee flexion strength manually.
Ligament Stress Testing <p>Lachman test</p>	
<p>Anterior drawer</p>	

(continued)

Table 41–6. Knee examination. (continued)

Maneuver	Description
Pivot shift 	<p>Used to determine the amount of rotational laxity of the knee. The patient is examined while lying supine with the knee in full extension. It is then slowly flexed while applying internal rotation and a valgus stress.</p> <p>Positive test: The clinician feels for a subluxation at 20–40 degrees of knee flexion. (The patient must remain very relaxed to have a positive test.)</p>
	
Valgus stress 	<p>Performed with the patient lying supine. The clinician should stand on the outside of the patient's knee. With one hand, the clinician should hold the ankle while the other hand is supporting the leg at the level of the knee joint. A valgus stress is applied at the ankle to determine pain and laxity of the medial collateral ligament. The test should be performed at both 30 degrees and 0 degrees of knee extension.</p> <p>Positive test: Pain and laxity of the medial collateral ligament with valgus stress.</p>

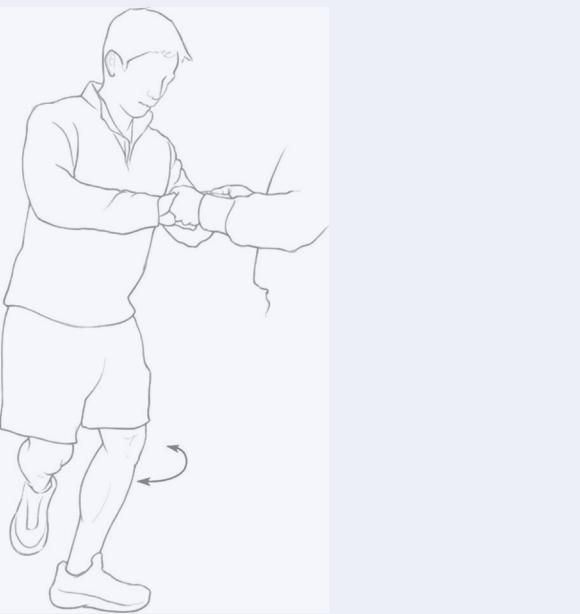
(continued)

Table 41–6. Knee examination. (continued)

Maneuver	Description
Varus stress 	Performed with the patient lying supine. For the right knee, the clinician should be standing on the right side of the patient. The left hand of the examiner should be holding the ankle while the right hand is supporting the lateral thigh. A varus stress is applied at the ankle to determine pain and laxity of the lateral collateral ligament. The test should be performed at both 30 degrees and 0 degrees of knee flexion. Positive test: Pain and laxity of the lateral collateral ligament with varus stress.
Meniscal Signs McMurray test	Performed with the patient lying supine. The clinician flexes the knee until the patient reports pain. For this test to be valid, it must be flexed pain-free beyond 90 degrees. Positive test: The clinician externally rotates the patient's foot and then extends the knee while palpating the medial knee for "click" in the medial compartment of the knee or pain reproducing pain from a meniscus injury. To test the lateral meniscus, the same maneuver is repeated while rotating the foot internally (53% sensitivity and 59–97% specificity).
Modified McMurray 	Performed with the patient lying supine and the hip flexed to 90 degrees. The knee is then flexed maximally with internal or external rotation of the lower leg. The knee can then be rotated with the lower leg in internal or external rotation to capture the torn meniscus underneath the condyles. Positive test: Pain over the joint line while the knee is being flexed and internally or externally rotated.

(continued)

Table 41–6. Knee examination. (continued)

Maneuver	Description
	Performed with the patient standing on one leg with knee slightly flexed. The patient is asked to twist the knee while standing on one leg. Positive test: Pain is elicited during twisting motion.
	

► Clinical Findings

A. Symptoms and Signs

Acute ACL injuries usually lead to acute swelling of the knee, causing difficulty with motion. After the swelling has resolved, the patient can walk with a “stiff-knee” gait or quadriceps avoidance gait because of the instability. Patients describe symptoms of instability while performing side-to-side maneuvers or descending stairs. Stability tests

assess the amount of laxity of the knee while performing these maneuvers. The Lachman test (84–87% sensitivity and 93% specificity) is performed with the patient lying supine and the knee flexed to 20–30 degrees (Table 41–6). The clinician grasps the distal femur from the lateral side and the proximal tibia with the other hand on the medial side. With the knee in neutral position, stabilize the femur, and pull the tibia anteriorly using a similar force to lifting a 10- to 15-pound weight. Excessive anterior translation of

the tibia compared with the other side indicates injury to the ACL. The anterior drawer test (48% sensitivity and 87% specificity) is performed with the patient lying supine and the knee flexed to 90 degrees (Table 41–6). The clinician stabilizes the patient's foot by sitting on it and grasps the proximal tibia with both hands around the calf and pulls anteriorly. A positive test finds ACL laxity compared with the unaffected side. The pivot shift test is used to determine the amount of rotational laxity of the knee (Table 41–6). The patient is examined while lying supine with the knee in full extension. It is then slowly flexed while applying internal rotation and a valgus stress. The clinician feels for a subluxation at 20–40 degrees of knee flexion. The patient must remain very relaxed to have a positive test.

B. Imaging

Plain radiographs are usually negative in ACL tears but are useful to rule out fractures. A small avulsion injury can sometimes be seen over the lateral compartment of the knee ("Segond" fracture) and is pathognomonic of an ACL injury. An ACL injury that avulsed the tibial spine can be seen in radiographs. MRI is the best tool to diagnose ACL tears and associated articular and meniscal cartilage issues. It has greater than 95% sensitivity and specificity for ACL tears.

Treatment

Most young and active patients will require surgical reconstruction of the ACL. Some data suggest that reconstruction within 5 months of the tear has better outcomes. However, a small randomized trial suggested that acute ACL injuries can be treated nonoperatively and delayed ACL reconstruction had similar outcomes to acute ACL reconstructions. Patients for whom the reconstruction is delayed, however, have more cartilage or meniscus problems at the time of surgery. Common surgical techniques use the patient's own tissue, usually the patellar or hamstring tendons (autograft), or use a cadaver graft (allograft) to arthroscopically reconstruct the torn ACL. Different patient groups experienced improved results with specific surgical graft choices. However, allografts do have a higher failure rate when compared with autografts. Recovery from surgery usually requires 6 months.

Nonoperative treatments are usually reserved for older patients or those with a very sedentary lifestyle. Physical therapy can focus on hamstring strengthening and core stability. An ACL brace can help stability. Longitudinal studies have demonstrated that nonoperative management of an ACL tear can lead to a higher incidence of meniscus tears. Cost-analysis studies have shown that early ACL reconstruction can be more beneficial than nonoperative treatment and delayed subsequent surgeries.

When to Refer

- Almost all ACL tears should be referred to an orthopedic surgeon for evaluation.
- Individuals with instability in the setting of a chronic ACL tear (greater than 6 months) should be considered for surgical reconstruction.

- Patients with an ACL tear and associated meniscus or articular injuries may benefit from surgery to address the other injuries.

Filbay SR et al. Evidence-based recommendations for the management of anterior cruciate ligament (ACL) rupture. *Best Pract Res Clin Rheumatol*. 2019;33:33. [PMID: 31431274]

Webster KE et al. What is the evidence for and validity of return-to-sport testing after anterior cruciate ligament reconstruction surgery? A systematic review and meta-analysis. *Sports Med*. 2019;49:917. [PMID: 30905035]

3. Collateral Ligament Injury

ESSENTIALS OF DIAGNOSIS

- ▶ Caused by a valgus or varus blow or stress to the knee.
- ▶ Pain and instability in the affected area.
- ▶ Limited range of motion.

General Considerations

The medial collateral ligament (MCL) is the most commonly injured ligament in the knee. It is usually injured with a valgus stress to the partially flexed knee. It can also occur with a blow to the lateral leg. The MCL is commonly injured with acute ACL injuries. The lateral collateral ligament (LCL) is less commonly injured, but this can occur with a medial blow to the knee. Since both collateral ligaments are extra-articular, injuries to these ligaments may not lead to any intra-articular effusion. Affected patients may have difficulty walking initially, but this can improve when the swelling decreases.

Clinical Findings

A. Symptoms and Signs

The main clinical findings for patients with collateral ligament injuries are pain along the course of the ligaments. The patient may have limited range of motion due to pain, especially during the first 2 weeks following the injury. The best tests to assess the collateral ligaments are the varus and valgus stress tests (Table 41–6). The test results can be graded from 1 to 3. Grade 1 is when the patient has pain with varus/valgus stress test but no instability. With grade 2 injuries, the patient has pain, and the knee shows instability at 30 degrees of knee flexion. In grade 3 injuries, the patient has marked instability but not much pain. The knee is often unstable at both 30 degrees and 0 degrees of knee flexion. The overall sensitivity of the tests is 86–96%.

B. Imaging

Radiographs are usually nondiagnostic except for avulsion injuries. However, radiographs should be used to rule out fractures that can occur with collateral ligament injuries. Isolated MCL injuries usually do not require evaluation by

MRI, but MRI should be used to evaluate possible associated cruciate ligament injuries. LCL or posterolateral corner injuries should have MRI evaluation to exclude associated injuries and to determine their significance.

► Treatment

The majority of MCL injuries can be treated with protected weight bearing and physical therapy. For grade 1 and 2 injuries, the patient can usually bear weight as tolerated with full range of motion. A hinged knee brace can be given to patients with grade 2 MCL tears to provide stability. Early physical therapy is recommended to protect range of motion and muscle strength. Grade 3 MCL injuries require long leg braces to provide stability. Patients can weight-bear, but only with the knee locked in extension with a brace. The motion can then be increased with the brace unlocked. Grade 3 injuries can take up to 6–8 weeks to heal. MCL injuries rarely need surgery. LCL injuries are less common but are usually associated with other ligament injuries (such as ACL and posterior cruciate ligament [PCL]). LCL injuries do not recover well with nonoperative treatment and usually require urgent surgical repair or reconstruction.

► When to Refer

- Symptomatic instability with chronic MCL tears or acute MCL tears with other ligamentous injuries.
- LCL or posterolateral corner injuries require urgent surgical repair or reconstruction (within 1 week).

Elkin JL et al. Combined anterior cruciate ligament and medial collateral ligament knee injuries: anatomy, diagnosis, management recommendations, and return to sport. *Curr Rev Musculoskelet Med*. 2019;12:239. [PMID: 30929138]

Grawe B et al. Lateral collateral ligament injury about the knee: anatomy, evaluation, and management. *J Am Acad Orthop Surg*. 2018;26:e120. [PMID: 29443704]

4. Posterior Cruciate Ligament Injury



ESSENTIALS OF DIAGNOSIS

- Usually follows anterior trauma to the tibia, such as a dashboard injury from a motor vehicle accident.
- The knee may freely dislocate and reduce.
- One-third of multi-ligament injuries involving the PCL have neurovascular injuries.

► General Considerations

The PCL is the strongest ligament in the knee. PCL injuries usually represent significant trauma and are highly associated with multi-ligament injuries and knee dislocations. More than 70–90% of PCL injuries have associated injuries to the posterolateral corner, MCL, and ACL. Neurovascular injuries occur in up to one-third of all knee dislocations or

PCL injuries. There should be high suspicion for neurovascular injuries and a thorough neurovascular examination of the limb should be performed.

► Clinical Findings

A. Symptoms and Signs

Most patients with acute injuries have difficulty with ambulation. Patients with chronic PCL injuries can ambulate without gross instability but may complain of subjective “looseness” and often report pain and dysfunction, especially with bending. Clinical examinations of PCL injuries include the “sag sign”; the patient is placed supine and both hips and knees are flexed to 90 degrees. Because of gravity, the posterior cruciate ligament-injured knee will have an obvious set-off at the anterior tibia that is “sagging” posteriorly. The PCL ligament can also be examined using the **posterior drawer test**; the patient is placed supine with the knee flexed to 90 degrees. In a normal knee, the anterior tibia should be positioned about 10 mm anterior to the femoral condyle. The clinician can grasp the proximal tibia with both hands and push the tibia posteriorly. The movement, indicating laxity and possible tear of the PCL, is compared with the uninjured knee (90% sensitivity and 99% specificity). A PCL injury is sometimes mistaken for an ACL injury during the anterior drawer test since the tibia is subluxed posteriorly in a sagged position and can be abnormally translated forward, yielding a false-positive test for an ACL injury. Pain, swelling, pallor, and numbness in the affected extremity may suggest a knee dislocation with possible injury to the popliteal artery. If the lateral knee is unstable with varus stress testing (Table 41–6), the patient should be assessed for a posterolateral corner injury, which consists of injuries to the lateral collateral ligament, popliteus tendon, and popliteofibular ligament. Injuries to the posterolateral corner usually require urgent surgical treatment.

B. Imaging

Radiographs are often nondiagnostic but are required to diagnose any fractures. MRI is used to diagnose PCL and other associated injuries.

► Treatment

Isolated PCL injuries can be treated nonoperatively. Acute injuries are usually immobilized using a knee brace with the knee extension; the patient uses crutches for ambulation. Physical therapy can help achieve increased range of motion and improved ambulation. Many PCL injuries are associated with other injuries and may require operative reconstruction.

► When to Refer

- The patient should be seen urgently within 1–2 weeks.
- Posterolateral corner injury requires urgent surgical reconstruction.
- Isolated PCL tears may require surgery if the tear is complete (grade 3) and the patient is symptomatic.

Badri A et al. Clinical and radiologic evaluation of the posterior cruciate ligament-injured knee. *Curr Rev Musculoskelet Med.* 2018;11:515. [PMID: 29987531]

Devitt BM et al. Isolated posterior cruciate reconstruction results in improved functional outcome but low rates of return to preinjury level of sport: a systematic review and meta-analysis. *Orthop J Sports Med.* 2018;6:2325967118804478. [PMID: 30386804]

5. Meniscus Injuries



ESSENTIALS OF DIAGNOSIS

- ▶ Patient may or may not report an injury.
- ▶ Joint line pain and pain with deep squatting are the most sensitive signs.
- ▶ Difficulty with knee extension suggests an internal derangement that should be evaluated urgently with MRI.

► General Considerations

The menisci act as shock absorbers within the knee. Injuries to a meniscus can lead to pain, clicking, and locking sensation. Most meniscus injuries occur with acute injuries (usually in younger patients) or repeated microtrauma, such as squatting or twisting (usually in older patients).

► Clinical Findings

A. Symptoms and Signs

The patient may have an antalgic (painful) gait and difficulty with squatting. He or she may complain of catching or locking of the meniscal fragment. Physical findings can include effusion or joint line tenderness. Patients can usually point out the area of maximal tenderness along the joint line. Swelling usually occurs during the first 24 hours after the injury or later. Meniscus tears rarely lead to the immediate swelling that is commonly seen with fractures and ligament tears. Meniscus tears are commonly seen in arthritic knees. However, it is often unclear whether the pain is coming from the meniscus tear or the arthritis.

Provocative tests, including the **McMurray test**, the **modified McMurray test**, and the **Thessaly test**, can be performed to confirm the diagnosis (Table 41–6). Most symptomatic meniscus tears cause pain with deep squatting and when waddling (performing a “duck walk”).

B. Imaging

Radiographs are usually normal but may show joint space narrowing, early OA changes, or loose bodies. MRI of the knee is the best diagnostic tool for meniscal injuries (93% sensitivity and 95% specificity). High signal through the meniscus (bright on T2 images) represents a meniscal tear.

► Treatment

Conservative treatment can be used for degenerative tears in older patients. The treatment is similar for patients with

mild knee OA, including analgesics and physical therapy for strengthening and core stability. A randomized controlled trial showed that physical therapy compared to arthroscopic partial meniscectomy had similar outcomes at 6 months. However, 30% of the patients who were assigned to physical therapy alone underwent surgery within 6 months.

Randomized studies have shown that arthroscopic surgery has no benefit over sham operations in patients who have degenerative meniscal tears, especially with imaging showing signs of osteoarthritis. Another randomized controlled trial found that patients with degenerative meniscus tears but no signs of arthritis on imaging treated conservatively with supervised exercise therapy had similar outcomes to those treated with arthroscopy at 2-year follow-up. There is crossover between the groups; patients can be treated with supervised exercise therapy first, and if they do not respond to nonoperative treatment, they can undergo meniscus surgeries. Acute tears in young and active patients with clinical signs of internal derangement (catching and swelling) and without signs of arthritis on imaging or patients with acute mechanical locking with a displaced meniscus can be best treated arthroscopically with meniscus repair or debridement. There is also growing evidence that untreated meniscus root tears can lead to accelerated osteoarthritic changes. Surgical treatment before cartilage breakdown is recommended for acute meniscus root injuries.

► When to Refer

- If the patient has symptoms of internal derangement suspected as meniscus injury. The patient should receive an MRI to confirm the injury.
- If the patient cannot extend the knee due to a mechanical block, the patient should be evaluated as soon as possible. Certain shaped tears on MRI, such as bucket handle tears, meniscus root injuries, are amenable to meniscal repair surgery.
- If the patient has not responded to physical therapy and nonoperative treatment and continues to have symptoms related to the torn meniscus.
- If the patient has MRI confirmation of acute meniscus root injuries.

Driban JB et al. Accelerated knee osteoarthritis is characterized by destabilizing meniscal tears and pre-radiographic structural disease burden. *Arthr Rheumatol.* 2019;71:1089. [PMID: 30592385]
Karia M et al. Current concepts in the techniques, indications and outcomes of meniscal repairs. *Eur J Orthop Surg Traumatol.* 2019;29:509. [PMID: 30374643]

6. Patellofemoral Pain



ESSENTIALS OF DIAGNOSIS

- ▶ Pain experienced with bending activities (kneeling, squatting, climbing stairs).
- ▶ Lateral deviation or tilting of the patella in relation to the femoral groove.

► General Considerations

Patellofemoral pain, also known as anterior knee pain, chondromalacia, or “runner’s knee,” describes any pain involving the patellofemoral joint. The pain affects any or all of the anterior knee structures, including the medial and lateral aspects of the patella as well as the quadriceps and patellar tendon insertions. The patella engages the femoral trochlear groove with approximately 30 degrees of knee flexion. Forces on the patellofemoral joint increase up to three times body weight as the knee flexes to 90 degrees (eg, climbing stairs), and five times body weight when going into full knee flexion (eg, squatting). Abnormal patellar tracking during flexion can lead to abnormal articular cartilage wear and pain. When the patient has ligamentous hyperlaxity, the patella can sublux out of the groove, usually laterally. Patellofemoral pain is also associated with muscle strength and flexibility imbalances as well as altered hip and ankle biomechanics.

► Clinical Findings

A. Symptoms and Signs

Patients usually complain of pain in the anterior knee with bending movements and less commonly in full extension. Pain from this condition is localized under the kneecap but can sometimes be referred to the posterior knee or over the medial or lateral inferior patella. Symptoms may begin after a trauma or after repetitive physical activity, such as running and jumping. When maltracking, palpable and sometimes audible crepitus can occur.

Intra-articular swelling usually does not occur unless there are articular cartilage defects or if OA changes develop. On physical examination, it is important to palpate the articular surfaces of the patella. For example, the clinician can use one hand to move the patella laterally, and use the fingertips of the other hand to palpate the lateral undersurface of the patella. Patellar mobility can be assessed by medially and laterally deviating the patella (deviation by one-quarter of the diameter of the kneecap is considered normal; greater than one-half the diameter suggests excessive mobility). The **apprehension sign** suggests instability of the patellofemoral joint and is positive when the patient becomes apprehensive when the patella is deviated laterally. The **patellar grind test** is performed by grasping the knee superior to the patella and pushing it downward with the patient supine and the knee extended, pushing the patella inferiorly. The patient is asked to contract the quadriceps muscle to oppose this downward translation, with reproduction of pain or grinding being the positive sign for chondromalacia of the patella. There are two common presentations: (1) patients whose ligaments and patella are too loose (hypermobility); and (2) patients who have soft tissues that are too tight, leading to excessive pressure on the joint.

Evaluation of the quadriceps strength and hip stabilizers can be accomplished by having the patient perform a one-leg squat without support. Normally, with a one-leg squat, the knee should align over the second metatarsal ray of the foot. Patients who are weak may display poor

balance, with dropping of the pelvis (similar to a positive hip Trendelenburg sign) or excessive internal rotation of the knee medially.

B. Imaging

Diagnostic imaging has limited use in younger patients and is more helpful in older patients to assess for OA or to evaluate patients who do not respond to conservative treatment. Radiographs may show lateral deviation or tilting of the patella in relation to the femoral groove. MRI may show thinning of the articular cartilage but is not clinically necessary, except prior to surgery or to exclude other pathology.

► Treatment

A. Conservative

For symptomatic relief, use of local modalities such as ice and anti-inflammatory medications can be beneficial. If the patient has signs of patellar hypermobility, physical therapy exercises are useful to strengthen the quadriceps (especially the vastus medialis obliquus muscle) to help stabilize the patella and improve tracking. There is consistent evidence that exercise therapy for patellofemoral pain syndrome may result in clinically important reduction in pain and improvement in functional ability. Lower quality research supports that hip and knee exercises are better than knee exercises alone. Strengthening the quadriceps and the posterolateral hip muscles such as the hip abductors that control rotation at the knee should be recommended. Support for the patellofemoral joint can be provided by use of a patellar stabilizer brace or special taping techniques (McConnell taping). Correcting lower extremity alignment (with appropriate footwear or over-the-counter orthotics) can help improve symptoms, especially if the patient has pronation or high-arched feet. If the patient demonstrates tight peripatellar soft tissues, special focus should be put on stretching the hamstrings, iliotibial band, quadriceps, calves, and hip flexors.

B. Surgical

Surgery is rarely needed and is considered a last resort for patellofemoral pain. Procedures performed include lateral release or patellar realignment surgery.

► When to Refer

Patients with persistent symptoms despite a course of conservative therapy.

Bogla LA et al. National Athletic Trainers’ Association Position Statement: management of individuals with patellofemoral pain. J Athl Train. 2018;53:820. [PMID: 30372640]

Crossley KM et al. Rethinking patellofemoral pain: prevention, management and long-term consequences. Best Pract Res Clin Rheumatol. 2019;33:48. [PMID: 31431275]

Saltychev M et al. Effectiveness of conservative treatment for patellofemoral pain syndrome: a systematic review and meta-analysis. J Rehabil Med. 2018;50:393. [PMID: 29392329]

7. Knee Osteoarthritis



ESSENTIALS OF DIAGNOSIS

- ▶ Degeneration of joint cartilage.
- ▶ Pain with bending or twisting activities.
- ▶ Swelling.
- ▶ Loss of active and passive range of motion in severe OA.

► General Considerations

The incidence of knee OA in the United States is 240 per 100,000 person-years; the prevalence of OA will likely grow to 70 million persons by 2030 as the number of persons over age 65 increases.

Cartilage loss and OA symptoms are preceded by damage to the collagen-proteoglycan matrix. The etiology of OA is often multifactorial including previous trauma, prior high-impact activities, genetic factors, obesity, and rheumatologic or metabolic conditions.

► Clinical Findings

A. Symptoms and Signs

OA usually causes pain in the affected joint with loading of the joint or at the extremes of motion. Mechanical symptoms—such as swelling, grinding, catching, and locking—suggest internal derangement, which is indicated by damaged cartilage or bone fragments that affect the smooth range of motion expected at an articular joint. Pain can also produce the sensation of “buckling” or “giving way” due to muscle inhibition (Tables 41–4, 41–5, and 41–6). As the joint degeneration becomes more advanced, the patient loses active range of motion and may lose passive range of motion as well.

As the condition worsens, patients with knee OA have an increasingly limited ability to walk. Symptoms include pain with bending or twisting activities, and going up and down stairs. Swelling, limping, and pain while sleeping are common complaints with OA, especially as it progresses.

B. Imaging

The most commonly recommended radiographs include bilateral weight-bearing 45-degree bent knee posteroanterior, lateral, and patellofemoral joint views (Merchant view). Radiographic findings include diminished width of the articular cartilage causing joint space narrowing, subchondral sclerosis, presence of osteophytes, and cystic changes in the subchondral bone. MRI of the knee is most likely unnecessary unless other pathology is suspected, such as ischemic osteonecrosis of the knee.

► Treatment

A. Conservative

Changes in the articular cartilage are irreversible. Therefore, a cure for the diseased joint is not possible, although

symptoms or structural issues can be addressed to try to maintain activity level. Conservative treatment for all patients with OA includes activity modification, therapeutic exercises, and weight loss. Lifestyle modifications also include proper footwear and avoidance of high-impact activities. Optimal exercise programs for knee OA should focus on improving aerobic capacity, quadriceps muscle strength, or lower extremity performance. Ideally, the program should be supervised and carried out three times a week.

Use of a cane in the hand opposite to the affected side is mechanically advantageous. Knee sleeves or braces provide some improvement in subjective pain symptoms most likely due to improvements in neuromuscular function. If patients have unicompartmental OA in the medial or lateral compartment, joint unloader braces are available to offload the degenerative compartment. Cushioning footwear and appropriate orthotics or shoe adjustments are useful for reducing impact to the lower extremities.

The first-line recommendation for pain management is topical nonsteroidal medication. Alternatively, topical capsaicin may be effective. Oral medications that have been shown to significantly improve pain include ibuprofen, naproxen, diclofenac, and celecoxib. If a traditional NSAID is indicated, the choice should be based on cost, side-effect profile, and adherence (Table 5–5). For patients with increased risk of gastrointestinal bleeding, a cyclooxygenase (COX)-2 inhibitor (ie, celecoxib) or adding a proton pump inhibitor to the NSAID is recommended. A COX-2 inhibitor is no more effective than traditional NSAIDs; it may offer short-term, but probably not long-term, advantage in preventing gastrointestinal complications. Acetaminophen has been shown to be less effective than NSAIDs but can be used in patients when NSAID use is contraindicated. Tramadol can be used appropriately in patients with severe OA as alternative to NSAIDs, while opioid use is now discouraged. Turmeric supplements have shown some benefit for OA. Glucosamine and chondroitin sulfate are supplements that have been widely used and marketed for OA. Despite some initial promise, the best-controlled studies indicate these supplements are ineffective as analgesics in OA. However, they have minimal side effects and may be appropriate if the patient experiences subjective benefit.

Knee joint corticosteroid injections are options to help reduce pain and inflammation and can provide short-term pain relief, usually lasting about 6–12 weeks. While intra-articular triamcinolone is still commonly used in knee arthritis, a randomized controlled trial showed that 2 years of intra-articular triamcinolone every 3 months, compared with intra-articular saline, resulted in significantly greater quantitative cartilage volume loss by MRI and no significant difference in knee pain. This finding suggests that regular use of corticosteroid injections for long-term treatment of knee osteoarthritis should be avoided.

Viscosupplementation using injections of hyaluronic acid-based products is controversial. Because reviews suggested that viscosupplementation has a questionably clinically relevant effect size and an increased risk of non-threatening adverse events, the American Academy of

Orthopedic Surgeons recommended that viscosupplementation should not be used in the treatment of knee OA. However, the American College of Rheumatology's 2012 OA guidelines still recommend the use of intra-articular hyaluronic acid injection for the treatment of OA of the knee in adults.

Platelet-rich plasma injections contain high concentration of platelet-derived growth factors, which regulate some biologic processes in tissue repair. A meta-analysis of 10 studies demonstrated that platelet-rich plasma injections reduced pain in patients with knee OA more efficiently than placebo and hyaluronic acid injections. However, 9 of the 10 studies had a high risk of bias, and the underlying mechanism of biologic healing is unknown. An FDA safety and efficacy study showed that leukocyte-poor PRP autologous conditioned plasma improved overall Western Ontario and McMaster Universities Arthritis Index scores by 78% from the baseline score after 12 months, compared to 7% for the placebo group, though the sample size was small (30 patients).

B. Surgical

Two randomized trials demonstrated that arthroscopy does not improve outcomes at 1 year over placebo or routine conservative treatment of OA. Joint replacement surgeries are effective and cost-effective for patients with significant symptoms or functional limitations, providing improvements in pain, function, and quality of life. Minimally invasive surgeries and computer-assisted navigation during operation are being investigated as methods to improve techniques (eg, accurate placement of the hardware implant) and to reduce complication rates; however, major improvements have yet to be demonstrated.

Knee realignment surgery, such as high tibial osteotomy or partial knee replacement surgery, is indicated in patients younger than age 60 with unicompartmental OA, who would benefit from delaying total knee replacement. Knee joint replacement surgery has been very successful in improving outcomes for patient with end-stage OA. Long-term series describe more than 95% survival rate of the implant at 15 years.

► When to Refer

Patients with sufficient disability, limited benefit from conservative therapy, and evidence of severe OA can be referred for joint replacement surgery.

Bannuru RR et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27:1578. [PMID: 31278997]

Honvo G et al. Update on the role of pharmaceutical-grade chondroitin sulfate in the symptomatic management of knee osteoarthritis. *Aging Clin Exp Res*. 2019;31:1163. [PMID: 31243744]

Paultre K et al. Therapeutic effects of turmeric or curcumin extract on pain and function for individuals with knee osteoarthritis: a systematic review. *BMJ Open Sport Exerc Med*. 2021;7:e000935. [PMID: 33500785]

Richardson C et al. Intra-articular hyaluronan therapy for symptomatic knee osteoarthritis. *Rheum Dis Clin North Am*. 2019;45:439. [PMID: 31277754]

Sharma L. Osteoarthritis of the knee. *N Engl J Med*. 2021;384:51. [PMID: 33406330]

Skou ST et al. Physical therapy for patients with knee and hip osteoarthritis: supervised, active treatment is current best practice. *Clin Exp Rheumatol*. 2019;37:112. [PMID: 31621559]

Vincent P. Intra-articular hyaluronic acid in the symptomatic treatment of knee osteoarthritis: a meta-analysis of single-injection products. *Curr Ther Res Clin Exp*. 2019;90:39. [PMID: 31289603]

ANKLE INJURIES

1. Inversion Ankle Sprains



ESSENTIALS OF DIAGNOSIS

- ▶ Localized pain and swelling.
- ▶ The majority of ankle injuries involve inversion injuries affecting the lateral ligaments.
- ▶ Consider chronic ankle instability or associated injuries if pain persists for > 3 months following an ankle sprain.

► General Considerations

Ankle sprains are the most common sports injuries seen in outpatient clinics. Patients usually report “turning the ankle” during a fall or after landing on an irregular surface such as a hole or an opponent’s foot. The most common mechanism of injury is an inversion and plantar flexion sprain, which injures the anterior talofibular (ATF) ligament rather than the calcaneofibular (CF) ligament. Other injuries that can occur with inversion ankle injuries are listed in Table 41–7. Women appear to sustain an inversion injury more frequently than men. Chronic ankle instability

Table 41–7. Injuries associated with ankle sprains.

Ligaments

- Subtalar joint sprain
- Sinus tarsi syndrome (ongoing anterolateral post-traumatic ankle pain)
- Syndesmotic (distal tibiofibular ligamentous) sprain
- Deltoid sprain
- Lisfranc (tarsometatarsal bony or ligamentous) injury

Tendons

- Posterior tibial tendon strain
- Peroneal tendon subluxation

Bones

- Osteochondral talus injury
- Lateral talar process fracture
- Posterior impingement (os trigonum)
- Fracture at the base of the fifth metatarsal
- Jones fracture (between base and middle of fifth metatarsal)
- Salter (growth plate) fracture (fibula)
- Ankle fractures

is defined as persistent complaints of pain, swelling, and “giving way” in combination with recurrent sprains for at least 12 months after the initial ankle sprain. Chronic ankle instability can occur in up to 43% of ankle sprains despite physical therapy, which makes appropriate attention to acute ankle sprains important.

► Clinical Findings

A. Symptoms and Signs

Symptoms following a sprain include localized pain and swelling over the lateral aspect of the ankle, difficulty weight bearing, and limping. On examination, there may be swelling or bruising over the lateral aspect of the ankle. The anterior, inferior aspect below the lateral malleolus is most often the point of maximal tenderness consistent with ATF and CF ligament injuries. The swelling may limit motion of the ankle.

Special stress tests for the ankle include the **anterior drawer test**; the clinician keeps the foot and ankle in the neutral position with the patient sitting, then uses one hand to fix the tibia and the other to hold the patient's heel and draw the ankle forward. Normally, there may be approximately 3 mm of translation until an endpoint is felt. A positive test includes increased translation of one foot compared to the other with loss of the endpoint of the ATF ligament.

Another stress test is the **subtalar tilt test**, which is performed with the foot in the neutral position with the patient sitting. The clinician uses one hand to fix the tibia and the other to hold and invert the calcaneus. Normal inversion at the subtalar joint is approximately 30 degrees. A positive test consists of increased subtalar joint inversion by greater than 10 degrees on the affected side with loss of endpoint for the CF ligament. In order to grade the severity of ankle sprains, no laxity on stress tests is considered a grade 1 injury, laxity of the ATF ligament on anterior drawer testing but a negative tilt test is a grade 2 injury, and both positive drawer and tilt tests signify a grade 3 injury. Difficulty jumping and landing within 2 weeks from the acute ankle sprain, abnormal postural or hip muscle control, or ligamentous laxity noted 8 weeks after injury are poor prognostic signs.

B. Imaging

Routine ankle radiographic views include the AP, lateral, and oblique (mortise) views. Less common views requested include the calcaneal view and subtalar view. The **Ottawa Ankle Rules** remain the best clinical prediction rules to guide the need for radiographs and have an 86–99% sensitivity and a 97–99% negative predictive value. If the patient is unable to bear weight immediately in the office setting or emergency department for four steps, then the clinician should check for (1) bony tenderness at the posterior edge of the medial or lateral malleolus and (2) bony tenderness over the navicular (medial midfoot) or at the base of the fifth metatarsal. If either malleolus demonstrates pain or deformity, then ankle radiographs should be obtained. If the foot has bony tenderness, obtain foot radiographs. An MRI is helpful when considering the associated injuries.

► Treatment

Immediate treatment of an ankle sprain follows the MICE mnemonic: *m*odified activities, *i*ce, *c*ompression, and *e*levation. NSAIDs are useful in reducing pain and swelling in the first 72 hours following the ankle sprain. Subsequent treatment involves protected weight bearing with crutches and use of an ankle stabilizer brace, especially for grade 2 and 3 injuries. Early motion is essential, and patients should be encouraged to do a program of exercises or physical therapy. Proprioception and balance exercises (eg, “wobble board”) are useful to restore function to the ankle and prevent future ankle sprains. There is strong evidence for bracing and moderate evidence for neuromuscular training in preventing recurrence of an ankle sprain. Chronic instability can develop after acute ankle sprain in 10–20% of people and may require surgical stabilization with ligament reconstruction surgery.

► When to Refer

- Ankle fractures.
- Recurrent ankle sprains or signs of chronic ligamentous ankle instability.
- No response after more than 3 months of conservative treatment.
- Suspicion of associated injuries.

Delahunt E et al. Risk factors for lateral ankle sprains and chronic ankle instability. *J Athl Train*. 2019;54:611. [PMID: 31161942]

Kaminski TW et al. Prevention of lateral ankle sprains. *J Athl Train*. 2019;54:650. [PMID: 31116041]

Mandegaran R et al. Beyond the bones and joints: a review of ligamentous injuries of the foot and ankle on (99m)Tc-MDP-SPECT/CT. *Br J Radiol*. 2019;92:20190506. [PMID: 31365277]

Vuurberg G et al. Diagnosis, treatment and prevention of ankle sprains: update of an evidence-based clinical guideline. *Br J Sports Med*. 2018;52:956. [PMID: 29514819]

2. Eversion (“High”) Ankle Sprains

ESSENTIALS OF DIAGNOSIS

- 
- Severe and prolonged pain.
 - Limited range of motion.
 - Mild swelling.
 - Difficulty with weight bearing.

► General Considerations

A syndesmotic injury or “high ankle” sprain involves the anterior *tibiofibular* ligament in the anterolateral aspect of the ankle, superior to the anterior *talofibular* (ATF) ligament. The injury mechanism often involves the foot being turned out or externally rotated and everted (eg, when being tackled). This injury is commonly missed or misdiagnosed as an ATF ligament sprain on initial visit.

► Clinical Findings

A. Symptoms and Signs

Symptoms of a high ankle sprain include severe and prolonged pain over the anterior ankle at the anterior tibiofibular ligament, worse with weight bearing. This is often more painful than the typical ankle sprain. The point of maximal tenderness involves the anterior tibiofibular ligament, which is higher than the ATF ligament. It is also important to palpate the proximal fibula to rule out any proximal syndesmotic ligament injury and associated fracture known as a “maisonneuve fracture.” There is often some mild swelling in this area, and the patient may or may not have an ankle effusion. The patient usually has limited range of motion in all directions. To perform the **external rotation stress test**, the clinician fixes the tibia with one hand and grasps the foot in the other with the ankle in the neutral position. The ankle is then dorsiflexed and externally rotated, reproducing the patient’s pain. (**Note:** The patient’s foot should have an intact neurovascular examination before undertaking this test.)

B. Imaging

Radiographs of the ankle should include the AP, mortise, and lateral views. The mortise view may demonstrate loss of the normal overlap between the tibia and fibula, which should be at least 1–2 mm. Asymmetry in the joint space around the tibiotalar joint suggests disruption of the syndesmotic ligaments. If there is proximal tenderness in the lower leg especially around the fibula, an AP and lateral view of the tibia and fibula should be obtained to rule out

a proximal fibula fracture. Radiographs during an external rotation stress test may visualize instability at the distal tibiofibular joint. MRI is the best method to visualize injury to the tibiofibular ligament and to assess status of the other ligaments and the articular cartilage.

► Treatment

Whereas most ankle sprains are treated with early motion and weight bearing, treatment for a high ankle sprain should be conservative with a cast or walking boot for 4–6 weeks. Thereafter, protected weight bearing with crutches is recommended until the patient can walk pain-free. Physical therapy can start early to regain range of motion and maintain strength with limited weight bearing initially.

► When to Refer

If there is widening of the joint space and asymmetry at the tibiotalar joint, the patient should be referred urgently to a foot and ankle surgeon. Severe or prolonged persistent cases that do not heal may require internal fixation to avoid chronic instability at the tibiofibular joint. Screw fixation remains the gold standard, although newer techniques with bioabsorbable constructs are emerging.

Chen ET et al. Ankle sprains: evaluation, rehabilitation, and prevention. Curr Sports Med Rep. 2019;18:217. [PMID: 31385837]
Nickless JT et al. High ankle sprains: easy to miss, so follow these tips. J Fam Pract. 2019;68:E5. [PMID: 31039220]

Sexual & Gender Minority Health

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HEALTH CARE FOR SEXUAL & GENDER MINORITY PATIENTS

► Definitions & Concepts

Gender identity is a person's internal sense of gender, which is independent from the sex assigned at birth. Gender is also independent from sexual orientation, which refers to one's sexuality and encompasses three dimensions: identity, behavior, and desire. The term **sexual and gender minorities (SGM)** refers to a broad group including lesbian women and gay men; bisexual, pansexual, and queer people; and transgender and gender non-binary people—also commonly referred to as "LGBTQ" or "LGBTQ+." The plus sign is inclusive of individuals of other identities such as agender, genderqueer, and polysexual.

Transgender people have a gender identity that differs from the sex which was assigned at birth, including those who identify as non-binary and those who have a gender identity that is neither man nor woman. Transmasculine will refer to those who have a male or masculine-spectrum gender identity but were assigned female at birth, and transfeminine will refer to those who have a female or feminine spectrum gender identity but were assigned male at birth. Cisgender refers to people who have a gender identity and birth assigned sex that are the same (ie, they are not transgender). Transgender people may also be sexual minorities (ie, lesbian, gay, bisexual, etc). For the sake of expediency in this chapter, the sections on sexual minority men and women omit the term "cisgender"; however, readers of these sections should take into consideration that, for example, gay transmasculine persons may have vaginal receptive sex with cisgender men as sexual partners, and therefore should be screened for contraception needs, and cisgender lesbian women may have transfeminine partners who retain their penis. Sexual *identities* include gay (those who are predominantly attracted to and/or sexually active with members of the same gender), bisexual (those who are attracted to and/or sexually active with someone of the same gender and another gender (historically men and women), and heterosexual or straight (someone who is attracted to and/or sexually active with people of another gender, historically the "opposite")

gender); however, several other terms may be used, and terminology changes over time. A growing number of people identify as pansexual, which describes an attraction to people of any gender—man, woman, or on the spectrum between the two. The term "queer" has been reclaimed by many SGM people to represent someone with a sexual orientation, gender identity, or gender expression (the external manifestation of gender) that differs from that of a cisgender, heterosexual person. Because of the historical legacy of this term as derogatory, however, it should not be used unless someone specifies this as their identity. Studies have demonstrated that there is a broad diversity among those who identify as SGM and that many people have multiple gender identities and/or sexual orientations.

Population estimates of SGM adults in the United States range from 4.5% to 6.8%, depending on definitions; reliable population estimates, however, are lacking because there are no consistently applied federal and other administrative survey methodologies. Data about SGM demographics depend on sampling methods and study questions; for example, individuals identify as SGM in higher rates when asked about lifetime versus current SGM identity, and when asked about attraction versus behavior. Population estimates of SGM persons reach 20% if the definition of SGM includes gay or bisexual identity, any same-sex attraction, or same-sex sex in the last year.

The three dimensions of sexual orientation—identity, behavior, and attraction—do not necessarily overlap. Health risk factors (like smoking) and outcomes have been found to be different among different dimensions. For example, in one national, probability-based survey, less than 50% of men who have sex with men (MSM) identified as gay and bisexual older adults with identity-attraction discordance were at higher risk for adverse smoking-related health consequences. The incomplete overlap of identity and behavior means that clinicians cannot rely upon self-reported identity to infer sexual behavior, and vice versa.

It is important to distinguish sexual orientation from gender identity. Knowing someone's gender identity does not identify one's sexual orientation. Just as cisgender people may be sexually attracted to and have sex with people of any gender, so too can transmasculine,

transfeminine, and non-binary people have partners of any gender. Routinely asking about sexual orientation, and when relevant for the clinical issue at hand, sexual behavior, helps build trust between the patient and clinician, ensures appropriate medical care (for example, appropriate screening tests for sexually transmitted infections [STIs] and family planning), and contributes to better health outcomes. To ensure that people feel welcomed, the clinician can ask people for their correct name and pronouns by first offering the clinician's correct name and pronouns. For example, the clinician may say "Hello, I'm Dr. (insert name), I use they/them pronouns. What name and pronouns would you like me to use for you?" Pronouns can also be included on ID badges. To inquire about gender identity and sex assigned at birth, the following questions are recommended: "What is your current gender identity?" and "What sex were you assigned at birth?" The clinician needs to remember that name and pronouns may differ from what one thinks may "match" what people say are their gender identity or sex assigned at birth or what is on "official" documentation, but the clinician must always use the name and pronouns that people shared.

Sexual orientation and gender identity may also change over time or be situational (such as during incarceration, in educational settings, etc). People may also hide their sexual orientation and gender identity from others, including clinicians, in order to avoid stigma and discrimination. Revealing one's sexual orientation, gender identity, or both is called "coming out." This process may occur at any point in life and may vary by context (for example, being "out" to family but not to coworkers).

Sexual orientation and gender identity can be fluid throughout a person's lifetime, and the binary concept of gender (that there are only girls and women or boys and men) is not evidence based. Some legal policies are moving to reflect this fluidity. In the United States, currently less than half of the states have three genders on legal documents: female, male, or non-binary (neither male nor female). These experiences and policies have implications for health screening for patients who receive care in health systems with pop-up reminders for sex-specific screening examinations such as mammography or prostate examinations.

Lunn MR et al. Using mobile technology to engage sexual and gender minorities in clinical research. PLoS One. 2019;14: e0216282. [PMID: 31048870]

McCabe SE et al. Tobacco use and sexual orientation in a national cross-sectional study: age, race/ethnicity, and sexual identity-attraction differences. Am J Prev Med. 2018;54:736. [PMID: 29656916]

Mishel E. Intersections between sexual identity, sexual attraction, and sexual behavior among a nationally representative sample of American men and women. J Official Statist. 2019; 35:859–84. [doi:10.2478/jos-2019-0036]

queer, involves the acknowledgment of the negative effects on health caused by discrimination and stigma. Ilan Meyer's theory of minority stress proposes that individuals who identify as a sexual minority experience chronic, additive, and unique stresses that stem from living in social conditions that are characterized by prejudice and discrimination; stressors include experiences of prejudice, expectations of rejection, the cognitive burden of deciding whether to come out in different circumstances, and internalized homophobia. SGM people are also underserved by the medical community and under-studied, with worse health outcomes compared to the heterosexual and cisgender populations. These experiences differ also according to racial and ethnic backgrounds; SGM people of color often fare worse. One reason for these disparities is that a previous negative experience in a clinician's office influences whether the patient will repeat a visit even for an acute medical event, which can delay care and result in advanced disease. One in three transgender people report delays in seeking care due to prior discrimination, and one in five report being refused medical care due to their transgender identity. SGM adults are twice as likely to delay care than non-SGM adults. Some of the disparate health outcomes are related to limited access to the health care system due to financial issues and lack of federal anti-discrimination protection at times compounded by multiple marginalized identities. LGBT people have higher rates of poverty, lower rates of home ownership, and higher rates of homelessness than non-LGBT people. These structural issues will take time to change. However, clinicians can impact the health outcomes of SGM people by ensuring that the clinical space is welcoming to people of all genders and sexual orientations (see below), obtaining comprehensive data on sexual orientation and gender identity, and being aware of the specific health needs of SGM people in order to advance the health of SGM patients. A study from Norway found that sympathetic environments can counteract minority stress and support overall health.

The vast majority of SGM patients would like to "come out" to their clinician. Many clinicians, however, are concerned that their patients would be offended if asked about sexual orientation and gender identity. It is important that clinicians overcome any discomfort and ask appropriate questions of their patients. There are useful video resources to help clinicians with these issues; one example is "Acknowledging Sex and Gender" Online Training video from the University of California San Francisco Center of Excellence for Transgender Health <https://prevention.ucsf.edu/transhealth/education/acknowledging-gender-sex>. Specific populations have additional barriers to disclosure and thus shared decision making, as shown in a study of Latinx SGM patients and their health care providers; suggestions for improvement include that professional interpreter services are SGM competent, that providers are aware of patients' varying social support from family members and that there is significant diversity among the Latinx SGM population. A study from South Africa found that discriminatory and prejudicial attitudes by health care providers, combined with their lack of competency and knowledge, are key reasons for SGM health disparities.

► Health Disparities & The Minority Stress Model

Providing compassionate and informed health care for SGM patients, which include but are not limited to persons who identify as lesbian, gay, bisexual, transgender, and

The SARS-CoV-2 pandemic most likely has disproportionately affected the SGM community; sexual orientation and gender identity (SOGI) data, however, were not considered in reporting prevalence or outcomes. With the increased homelessness and poverty, SGM people are a vulnerable community in the pandemic. One study documented that coincident with the pandemic, there is increased depression and anxiety within the SGM community in persons who did not have preexisting anxiety or depression. A significant number of front-line clinicians are from the SGM community, and their deaths have often been openly reported, which would have been rare even 10 years ago.

Flentje A, Obedin-Maliver J et al. Depression and anxiety changes among sexual and gender minority people coinciding with onset of COVID-19 pandemic. *J Gen Intern Med*. 2020;35:2788. [PMID: 32556877]

Lunn MR et al. Sociodemographic characteristics and health outcomes among lesbian, gay, and bisexual U.S. adults using Healthy People 2020 leading health indicators. *LGBT Health*. 2017;4:283. [PMID: 28727950]

Müller A. Scrambling for access: availability, accessibility, acceptability and quality of healthcare for lesbian, gay, bisexual and transgender people in South Africa. *BMC Int Health Hum Rights*. 2017;17:16. [PMID: 28558693]

The Williams Institute, UCLA School of Law. LGBT People and Housing Affordability, Discrimination and Homelessness. 2020 Apr. <https://williamsinstitute.law.ucla.edu/publications/lgbt-housing-instability/>

clinical practice guidelines, where applicable; and (12) if all gender bathrooms are not available, a posting states that patients are welcome to use either the women's or men's bathroom and the patient can determine which bathroom to use. One exercise is to look at clinic materials (ie, signs, posters, brochures, magazines, intake forms, etc) and see if materials presume heterosexual behavior and gender conformity (heteronormative). Often, materials discussing anatomy, sex, family planning, conception, pregnancy, and birth presume that everyone is cisgender, White, and primarily English speaking. If so, find or create more broadly inclusive materials to replace them.

National LGBT Cancer Network. Cultural competency in-person trainings and on-line materials, updated 2017. <https://cancer-network.org/programs/cultural-competency-training>
 National LGBT Education Center. Ten things: creating inclusive health care environments for LGBT people. July 2015. <http://www.lgbthealtheducation.org/wp-content/uploads/Ten-Things-Brief-Final-WEB.pdf>

► Obtaining Sexual History From SGM Patients

The core history and physical examination is not different for SGM in comparison to other patients. Clinicians should approach each patient as an individual, using patients' correct pronouns, using appropriate terminology, respecting the diversity of gender identity as well as the differing desires for gender affirming treatments, and performing a physical examination noting anatomic changes from any prior gender affirming treatment. As with all adolescent or adult patients, a complete medical history should include a comprehensive sexual history. Clinicians may wish to preface discussion of the patient's sexual history with a statement indicating that this information is confidential and is important in order to provide optimal health care. However, patients should not be expected to discuss their gender identity or transition in detail unless it is relevant to the current visit. In addition, it is crucial that clinicians understand that transgender patients may have physical appearances (gender expression), names, and/or pronouns that do not reflect their legal names or sex marker, as listed on identity documents. Staff members must learn how to elicit patients' names and correct pronouns so that these can be used consistently.

Key data to gather in a relevant sexual history include sexual function and satisfaction; number of partners if the patient is sexually active; the gender(s) of the patient's sexual partner(s); and the potential to conceive an unplanned pregnancy with the sexual partner(s). It should be noted that "sex" means different things to different people. Therefore, clinicians should determine the types of sexual practices the patient engages in (for example, oral sex, penile insertive anal sex, and/or receptive anal sex, penis-in-vagina sex, fingers-in-anus sex) acknowledging these may not line up with clinicians' assumptions based on someone's sexual orientation. Additional key questions include how often condoms are used, if at all, for the different sexual practices the patient engages in; and whether or not drugs and/or alcohol are consumed in conjunction with sex. Clinicians should also establish whether there is a

► Making Clinical Environments Welcoming to All SGM Patients

Part of serving SGM patients is to create a welcoming clinical space where each person is cared for and respected for **all** of who they are—including their sexual orientation, gender identity, and gender expression while considering other key aspects of their identities and lived experience like race and ethnicity, age, educational level, geography and geo-political context, and primary language. The use of people's correct names and pronouns throughout encounters is critical (see above). Implementation of comprehensive care including acknowledging, respecting, and specifying care as needed for someone based on their sexual orientation, gender identity, gender expression, and correct names and pronouns necessitates system change in many clinical settings. This includes making sure that (1) senior leadership is involved; (2) nondiscrimination policies are in place, are followed, and are prominently displayed; (3) open visitation policies are concordant with patients' choice of visitors; (4) outreach and engagement efforts are made for SGM patients; (5) staff receive culturally affirming training in the care of SGM people; (6) processes, forms, artwork, and reading materials reflect the diversity of SGM people; (7) data are collected about both sexual orientation and gender identity (including names and pronouns) in an open and nonjudgmental manner; (8) patients are routinely asked about their sexual health histories; (9) clinical care and services include prevention and wellness care with available family planning services and behavioral health services; (10) SGM staff are recruited and trained; (11) preventive care is concordant with

history of STIs because a positive history may have implications for medical follow-up and sexual risk assessment (eg, frequency of screening, syphilis serologies, chlamydia and gonorrhea testing, and discussion about HIV preexposure prophylaxis [PrEP]). For example, a recent diagnosis of syphilis would indicate the need for rapid plasma reagin (RPR) titer monitoring to ensure adequate treatment and would prompt consideration of PrEP due to the association of syphilis with HIV infection.

The Fenway Institute, which specializes in SGM health and health care, proposes using the following statement and follow-up questions:

"I am going to ask you some questions about your sexual health and sexuality that I ask all my patients. The answers to these questions are important for me to know how to help keep you healthy. Like the rest of this visit, this information is strictly confidential unless you tell me you are planning to harm yourself or someone else or describe someone else harming you."

Evidence suggests that most individuals are ready and willing to disclose to sensitive providers who make it clear the intent behind their questions. Additional questions include the following:

1. "Do you have a partner or a spouse?" or "Are you currently in a relationship?"
2. "When was the last time you had sex?"
3. "What is/are the gender(s) of your sexual partner(s)?"
4. "What body parts of yours touch which body parts of your partners?"
5. "How many people have you had sex with during the last year?"
6. "Do you have any desires regarding sexual intimacy that you would like to discuss?"

Rather than considering this a one-time intervention, it should be thought of as a process that is assessed over time and at critical junctures and changes in health status.

The Association of American Medical Colleges (AAMC) has created a series of online videos that highlight gender and sexual history taking (<https://www.aamc.org/initiatives/diversity/450468/gender-and-sexual-history1.html> and <https://www.aamc.org/initiatives/diversity/450470/gender-and-sexual-history2.html>); and ineffective history taking (<https://www.aamc.org/initiatives/diversity/450472/ineffective-history-taking.html>).

Centers for Disease Control and Prevention (CDC). A guide to taking a sexual history. <http://www.cdc.gov/std/treatment/sexualhistory.pdf>

Roszman K et al. "The doctor said I didn't look gay": young adults' experiences of disclosure and nondisclosure of LGBTQ identity to health care providers. *J Homosex*. 2017;64:1390. [PMID: 28459379]

assigned at birth as well as chosen name and pronouns. Chosen name and pronoun functionality should be displayed in all banners, schedules, and other viewing screens. Transgender persons can be identified within the EMR that supports the data collection of gender as separate from sex assigned at birth, by identifying those individuals whose entries for gender identity and birth sex differ. Collecting gender identity and sex assigned at birth data are critical to understanding the population of people in care within a health system.

Assessment and documentation in the EMR of a patient's sexual orientation and gender identity has been advocated in the United States by the National Academy of Medicine, the Joint Commission, and the Health Resources and Services Administration as fundamental to improving access to and quality of care for SGM people. However, there are risks for SGM people with having their sexual orientation and gender identity documented in the EMR. Examples of such risks include housing, child custody, and adoption discrimination. As of June 2020, the US Supreme Court determined that being fired on the basis of sexual orientation and/or transgender identity violated Title VII prohibition of discrimination on the basis of sex; however, there are still no federal protections against discrimination in housing, education, loans, or many other services. Further, same-sex relations are criminalized in over 72 countries. Gender identity is likewise insufficiently protected. Therefore, although sexual orientation and gender identity are critical to caring for the whole person, discussing with patients before documenting in the EMR is best practice.

Deutsch MB et al. Electronic medical records and the transgender patient: recommendations from the World Professional Association for Transgender Health EMR Working Group. *J Am Med Inform Assoc*. 2013;20:700. [PMID: 23631835]

Deutsch MB et al. Electronic health records and transgender patients—practical recommendations for the collection of gender identity data. *J Gen Intern Med*. 2015;30:843. [PMID: 25560316]

Grasso C et al. Planning and implementing sexual orientation and gender identity data collection in electronic health records. *J Am Med Inform Assoc*. 2019;26:66. [PMID: 30445621]

Polikoff ND. Neglected lesbian mothers. *Family Law Quarterly*. 2018;52:87.

► Family Planning

A. Pregnancy Prevention

Comprehensive family planning for SGM people is important to address, so that all pregnancies are intended if at all possible. Since one's sexual orientation and gender identity do not determine sexual partners, all individuals should be asked about family building intentions as well as contraception if pregnancy is undesired and their sexual activities that put them at risk for pregnancy.

The majority of lesbian women have been sexually active with men at some point in their lives (85–90%), and 30% of self-identified adult lesbians are currently sexually active with men as well as with women. Compared to heterosexual female youth, fewer lesbian and bisexual youth use highly reliable contraception. On multiple surveys, one

► The Electronic Medical Record

Electronic medical record (EMR) systems should include functionality for the recording of gender identity and sex

of the reasons that lesbians do not access gynecologic care is the assumption by clinicians that they are heterosexual, and the (insensitive) advocacy of birth control in that assumptive atmosphere about their sexuality (ie, heteronormative). On the other hand, multiple studies show that the unintended pregnancy rate of self-identified lesbian and bisexual youth is higher than that of the comparison heterosexual female youth. Unintended pregnancy risk continues into adulthood with one sample from the Chicago Health and Life Experiences of Women survey reporting 24% of sexual minority women having had unintended pregnancies. Sexual minority women also suffer higher rates of sexual assault compared with heterosexual women. If it has been determined that the patient self-identifies as a lesbian woman and is having (penis-in-vagina) sex with men, one suggested question might be, "Are you planning to get pregnant this year?" If the answer is no, this is an opportunity to explain that studies show a higher unintended rate of pregnancy in lesbian youth and to review effective contraception options. It is also a good time to talk about protection from STIs when having sex with men (ie, discuss condoms). As with any person engaging in penis-in-vagina sex, experts recommend additional contraceptives to condoms. Condoms are only 80% reliable in preventing pregnancy with typical use. Long-acting reversible contraceptives, which are not patient or sexual act dependent and function effectively despite alcohol or other substance use, are especially important to consider. Long-acting reversible contraceptives such as an etonorgestrel subdermal implant in the arm (0.05% annual failure) or either the copper (0.3% annual failure) or levonorgestrel (0.2% annual failure) intrauterine devices are highly effective and typical use is generally equivalent to ideal use.

Anyone with a vagina, uterus, ovaries, and fallopian tubes can potentially become pregnant if they engage in penis-in-vagina sex. Transfeminine persons (women who were assigned male sex at birth) and non-binary individuals who have a penis and testes may still produce sperm capable of fertilizing an oocyte even if using gender affirming hormones. For transmasculine persons and non-binary individuals who were assigned female sex at birth, contraception is important even if there is testosterone-induced amenorrhea; testosterone is not a reliable form of contraceptive. To underscore the point, transmasculine persons taking testosterone (even if amenorrheic) who have a uterus and ovaries and are sexually active with sperm involved should use any of the contraceptive methods available for cisgender women if they want to avoid a pregnancy. There are multiple case reports of transmasculine persons who have unintended pregnancies while taking testosterone. Since testosterone is a teratogen and no studies have been done to assess children born to gestational parents using testosterone, those who become pregnant while taking testosterone should receive counseling early in the pregnancy about their options. Little is known about contraceptive preferences and use profiles among transmasculine persons and non-binary people who were female sex assigned at birth.

A recent study evaluated pregnancy termination for transgender, non-binary, and gender expansive people and

found that the majority preferred medication abortion, due to their belief that it was the least invasive, although the majority of the respondents had undergone a surgical abortion. Respondents most frequently recommended that abortion clinics adopt gender-neutral or gender-affirming intake forms, that providers use gender-neutral language, and that greater privacy be incorporated into the clinic.

The AAMC has produced a noteworthy video about family counseling and coming out (<https://www.aamc.org/initiatives/diversity/450466/family-counseling.html>).

- Blunt-Venti HD et al. Contraceptive use effectiveness and pregnancy prevention information preferences among heterosexual and sexual minority college women. *Womens Health Issues*. 2018;28:342. [PMID: 29666034]
- Jones RK et al. Sexual orientation and exposure to violence among U.S. patients undergoing abortion. *Obstet Gynecol*. 2018;132:605. [PMID: 30095763]
- Light A et al. Family planning and contraception use in transgender men. *Contraception*. 2018;98:266. [PMID: 29944875]
- Moseson H et al. Abortion experiences and preferences of transgender, nonbinary, and gender-expansive people in the United States. *Am J Obstet Gynecol*. 2021;224:376.e1. [PMID: 32986990]
- Porsch L et al. Contraceptive use by women across multiple components of sexual orientation: findings from the 2011–2017 National Survey of Family Growth. *LGBT Health*. 2020;7:321. [PMID: 32808867]

B. Family Building

Family building should be discussed with all patients, regardless of sexual orientation or gender identity. Options include foster-parenting or adoption (in some countries these options are not open to SGM persons), co-parenting partners' child/children, becoming pregnant, contracting with a surrogate, or step-parenting. Some fertility practices refuse to assist SGM people with conception even if it is legal. The American College of Obstetricians and Gynecologists published Committee Opinion No. 749 in 2018, reaffirming their stance that no matter how a child comes into a family, all children and parents deserve equitable protections and access to available resources to maximize the health of that family unit. "Obstetricians-gynecologists should recognize the diversity in parenting desires that exists in the lesbian, gay, bisexual, transgender, queer, intersex, asexual and gender nonconforming communities and should take steps to ensure that clinical spaces are affirming and open to all parties, such that equitable and comprehensive, reproductive health care can meet the needs of these communities."

It is estimated that approximately 30% of SGM people are parents. The paths to parentage may differ broadly and include dependence on personal desires, organs, and gametes of the person and those of a partner(s) if any; any biologic/medical constraints; and legal/political options for adoption. Many options exist for conception; patients may ask the clinician for an opinion and to guide them to resources. Many patients may decide to have inseminations with an unknown donor from a sperm bank (some unknown donors sign a release so that the child may contact the donor when the child reaches 18 years old), and

some may decide to involve a known sperm donor. Most sperm banks are regulated in regard to the administration of medical history forms, the testing of sperm for STIs, and the performance of genetic screening. Known donors may have risk factors but are not routinely screened. It is important for future parents to be as informed as they can be about the legal implications of each option. In some states and countries, unless the insemination with known donor sperm takes place in the office of a physician, the known donor has full legal rights as well as financial responsibilities for the offspring. In one study of 129 lesbian mothers with 77 index offspring, 77.5% of the mothers were satisfied with the type of donor chosen (36% had chosen known sperm donors, 25% open-identity donors, and 39% unknown donors). Donor access and custody concerns were the primary themes mentioned by lesbian mothers regarding their (dis)satisfaction with the type of sperm donor they had selected.

Some lesbian women and couples in whom both partners have a uterus and ovaries decide to do “co-in vitro fertilization (IVF),” which is also known as “reciprocal IVF” or in some cases “co-maternity” in which one partner provides an egg, it is fertilized in the laboratory with sperm of a known or unknown donor, and then the other partner carries the pregnancy. Lactation for the nongestating parent can sometimes be induced by using a protocol that stemmed originally from the experiences of adoptive mothers who were motivated to breastfeed. Lactation has been achieved for transmasculine and transfeminine persons as well. Many SGM people delay childbearing until later in life, which has been demonstrated in lesbian women, and then the issues of fertility, pregnancy loss, and birth defects increase. Pregnancy outcomes of bisexual and lesbian women compared to heterosexually identified women include increased risk of miscarriage (odds ratio [OR] 1.77) and stillbirth (OR 2.85), as well as very preterm birth (OR 1.84).

There have been many studies on the overall outcomes of children of lesbian women, all of which have been favorable when comparing their children to children raised by heterosexual parents, despite the stigma the children may experience of having same-sex parents. Using the 2011–2012 National Survey of Children’s Health data set from the United States, children with female same-sex parents and different-sex parents demonstrated no differences in outcomes (spouse-partner relationships, emotional difficulties, coping behaviors, and learning behavior).

Biologic options for pregnancy for cisgender gay men or transfeminine persons include conceiving with someone who may or may not be interested in co-parenting with them, or contracting with a friend, relative, or surrogate to carry the pregnancy after the sperm and a donor egg are fertilized and placed in the uterus of the surrogate. For transgender people, there are other options based on the organs they currently have. Prior to initiation of any gender affirming hormones or gender affirming surgical procedures, a consultation with either an obstetrician/gynecologist or a reproductive endocrinologist to discuss fertility preservation and future genetic offspring is encouraged. Reproductive planning is often not a priority for a transitioning youth but may become a desire in the future and may also be a priority for potential grandparents. Options

are limited for transgender youth who have not undergone endogenous puberty before either starting gender affirming hormones (with estrogen or testosterone) or puberty blockers and then going directly to estrogen or testosterone. The only future fertility option is either testicular or ovarian tissue cryopreservation, which is considered experimental. For transfeminine persons and gender non-binary individuals who were male sex assigned at birth and who have reached adulthood after endogenous puberty, sperm can be stored ideally prior to the initiation of estrogen. Of note, though some transfeminine persons still produce sperm even after long-term estrogen exposure, it is recommended that sperm cryopreservation occur prior to hormone start because the effect on fertility is hard to quantify and coming off hormones can often be dysphoric. For transmasculine persons and non-binary individuals who were female sex assigned at birth and have gone through endogenous puberty, next steps in genetic parentage will be based on the desire to carry a pregnancy and whether or not they have started gender affirming hormones. Options include penis-in-vagina sex, intravaginal insemination, intrauterine insemination, and egg cryopreservation for the individual, a partner, or surrogate to carry. If a hysterectomy is planned as part of gender affirmation, discussion of whether ovaries are left in place should occur in light of consideration of future genetic parentage as well as future hormone regulation versus the risk of future ovarian cancer. In one study in Australia, however, only 7% of transgender and non-binary adults had undertaken fertility preservation yet 95% said that fertility preservation should be offered to all transgender and non-binary people. Participants who viewed genetic relatedness as important were more likely to have undertaken fertility preservation. Perinatal care providers should also ensure that all components of perinatal care are welcoming to SGM people. A 2019 case study of a 32-year-old man who came to the emergency department with abdominal pain and hypertension illustrates the limits of classification and gender that is taught to health professionals. Even though the patient explained that he was a transman and his human chorionic gonadotropin level was elevated, he did not receive immediate care as indicated for possible obstetrical complications, including preterm labor or placental abruption. He delivered a stillborn infant hours later.

All SGM persons planning a pregnancy should be encouraged to consult with a family attorney prior to conception, and if partnered, the partner needs to be aware of their rights and responsibilities. The law has not kept up with the variety of family constellations that are seen in SGM families. Examples of these constellations include two gay cisgender fathers parenting together, each using the same egg donor so that their children are half-siblings biologically; a lesbian couple composed of a transfeminine person and cisgender woman where one partner provides the sperm and another provides the egg and carries the pregnancy; a straight cisgender father parenting with a lesbian cisgender mother; a lesbian cisgender couple with the sperm donor being the brother of the parent who did not provide the egg so one mother is genetically related via the egg and the other mother is genetically related to the

sperm (her brother's) thus being a biologic aunt; two cisgender lesbians each carrying a pregnancy conceived with their own eggs and using the same sperm donor so that their children are half-siblings; and two gay men where one is a cisgender man and provides the sperm and one is a transmasculine person and provides the egg and a surrogate carries the pregnancy.

- Baiocco R et al. Same-sex and different-sex parent families in Italy: is parents' sexual orientation associated with child health outcomes and parental dimensions? *J Dev Behav Pediatr.* 2018;39:555. [PMID: 29781831]
- Everett BG et al. Sexual orientation disparities in pregnancy and infant outcomes. *Matern Child Health J.* 2019;23:72. [PMID: 30019158]
- Hahn M et al. Providing patient-centered perinatal care for transgender men and gender-diverse individuals: a collaborative multidisciplinary team approach. *Obstet Gynecol.* 2019; 134:959. [PMID: 31599839]
- Kim A et al. Lesbian women undergoing assisted reproduction: diverse but not different. *Obstet Gynecol.* 2020;136:543. [PMID: 32769644]
- Reisman T et al. Case report: induced lactation in a transgender woman. *Transgend Health.* 2018;3:24. [PMID: 29372185]
- Stroumsa D et al. The power and limits of classification—a 32-year-old man with abdominal pain. *N Engl J Med.* 2019; 380:1885. [PMID: 31091369]

HEALTH CARE FOR LESBIAN & BISEXUAL WOMEN

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Cisgender lesbian and bisexual women are addressed together in this section since most medical literature does not delineate clearly enough between lesbian and bisexual cisgender women. Current medical literature also does not consider the intersection of sexual orientation and gender identity explicitly enough to evaluate the specific health needs and concerns of lesbian and bisexual women who are of transgender experience. In the United States, women in same-sex couples are less likely to have primary care providers, get nonurgent medical care when needed, see a specialist, and feel that doctors spent enough time with them. This is true worldwide with variability depending on the local sociopolitical climate. In countries with more restrictive laws and policies, health disparities are likely greater. A study in Lebanon noted that significantly more sexual minority women reported having trouble accessing health care than heterosexual women, and a meta-analysis of southern African countries outlined the unique health challenges faced by sexual minority women, including social exclusion and invisibility, criminalization, and systematic homophobic sexual assault. Limited clinician training likely exacerbates the lack of preparedness to care for sexual minority women.

- Gereige JD et al. The sexual health of women in Lebanon: are there differences by sexual orientation? *LGBT Health.* 2018;5:45. [PMID: 29130791]

► Health Disparities Affecting Lesbian & Bisexual Women

Health disparities exist across the life span for lesbian and bisexual women compared to heterosexual women. The following are increased among lesbian and bisexual women: childhood physical abuse in the home, childhood sexual abuse, substance use including alcohol and tobacco, chlamydial infection as teens and young adults, sexual assault, depression, disabilities, increased body mass index (BMI), intimate partner violence, threats and violence outside the home, asthma, and cardiovascular disease (CVD). Sexual dysfunction for lesbian and bisexual women is seen less often or as often as heterosexual women but is under-studied and likely assessed at rates lower than among heterosexual women. A high risk of sexual dysfunction can be detected by a single question regarding sexual function: "Do you have any questions or concerns about your sexuality or sexual health?" Studies of Irish SGM elders reveal concerns about residential care outside of their own home as well as respect by health professionals; similarly, there are concerns about home services for lesbian and bisexual women in Canada and the United States. Lesbian and bisexual women have fewer children available to help them as they age compared to heterosexual women. Therefore, it is critical that health care providers identify health decision makers for all patients, including lesbian and bisexual women, who may have more "family of choice" members versus "family of origin" members who may be estranged. This is especially important since same-sex/same-gender marriage is not allowed in many countries and is still considered socially unacceptable in many areas of the United States. To avoid conflict during critical decision-making moments, the health decision maker needs to be identified on the medical record after a private conversation with the patient. In one survey, only about 50% of same-sex couples who desired their partner to be the health decision maker had appropriate forms, and even if married, advance directives should be completed given past visitation denials. Many notable legal cases, including that of Sharon Kowalski and Karen Thompson, have documented the struggles that same-sex partners can face regarding visitation and appropriate recognition during end-of-life care or critical medical decision making when these documents have not been completed. Elder abuse screening also needs to be done, since the incidence is unknown in this population.

Kortes-Miller K et al. Dying in long-term care: perspectives from sexual and gender minority older adults about their fears and hopes for end of life. *J Soc Work End Life Palliat Care.* 2018;14:209. [PMID: 30457453]

Meads C et al. A systematic review of sexual minority women's experiences of health care in the UK. *Int J Environ Res Public Health.* 2019;16:E3032. [PMID: 31438599]

► Prevention of Cardiovascular Disease

The risk of CVD appears to be higher in sexual minority women compared with heterosexual peers; information on cardiovascular disease outcomes is limited, however, and many studies rely on self-report rather than objective

measures. Studies suggest that CVD risk is most influenced by psychosocial stress (ie, cumulative minority stress). In one study, lesbian and bisexual women were 14% older in vascular terms than their chronological age, which was 6% greater than that of their heterosexual counterparts; the risk was not fully explained by excessive smoking or alcohol use. Data from the Behavioral Risk Factor Surveillance System (2014–2016) showed that sexual minority women, compared with their heterosexual counterparts, had increased modifiable CVD risk factors of mental distress (lesbian adjusted odds ratio [AOR] 1.37; bisexual AOR 2.33), current smoking (lesbian AOR 1.65; bisexual AOR 1.29), heavy drinking (lesbian AOR 2.01; bisexual AOR 2.04), and obesity (lesbian AOR 1.50; bisexual AOR 1.29). Sexual minority women may have higher prevalence of hypertension compared with heterosexual counterparts. Sexual minorities, particularly bisexuals, were less likely than heterosexual peers to use statins for primary prevention but not secondary prevention, potentially highlighting a gap in access. Data from the Chicago Health and Life Experiences of Women study and the National Health Interview Survey found cardiometabolic risk factors (hypertension, diabetes, and obesity) and CVD outcomes, respectively, varied by sexual orientation and race/ethnicity highlighting the importance of intersectional assessments and interventions that account for sexual orientation, race, and ethnicity.

Caceres BA et al. Cardiovascular disease disparities in sexual minority adults: an examination of the Behavioral Risk Factor Surveillance System (2014–2016). *Am J Health Promot.* 2019; 33:576. [PMID: 30392384]

Caceres BA et al. Lifetime trauma and cardiometabolic risk in sexual minority women. *J Womens Health (Larchmt).* 2019; 28:1200. [PMID: 31099702]

Caceres BA et al. Racial/ethnic differences in cardiometabolic risk in a community sample of sexual minority women. *Health Equity.* 2019;3:350. [PMID: 31312782]

Caceres BA et al. Assessing and addressing cardiovascular health in LGBTQ adults: a scientific statement from the American Heart Association. *Circulation.* 2020;142:e321. [PMID: 33028085]

Guo Y et al. Statin use for atherosclerotic cardiovascular disease prevention among sexual minority adults. *J Am Heart Assoc.* 2020;9:e018233. [PMID: 33317368]

smoking behaviors for young LGB women included connections with other SGM people. Significant racial/ethnic differences exist; Asian and Pacific Islander lesbian and bisexual women have four times higher odds of smoking than heterosexual Asian and Pacific Islander women.

Both traditional smoking cessation programs and targeted SGM programs are effective for SGM people. A review of smoking cessation programs for LGBTI (I = intersex) people found that with cultural modifications for LGBTI people, 61% had quit at the end of interventions and this stabilized to 39% at 3–6 months. In Canada, 24 focus groups in Toronto and Ottawa detailed eight overarching themes that would be important to them in a smoking intervention: (1) be LGBTQ+ specific; (2) be accessible in terms of location, time, availability, and cost; (3) be inclusive, relatable, and highlight diversity; (4) incorporate LGBTQ+ peer support and counseling services; (5) integrate other activities beyond smoking; (6) be positive, motivational, uplifting, and empowering; (7) provide concrete coping mechanisms; and (8) integrate rewards and incentives. Other studies have corroborated that both SGM-specific (such as relation to “coming out,” different norms and acceptability of smoking among SGM communities, or SGM-related minority stress) and previously identified factors seen in other populations (such as self-efficacy around quitting) are important to support SGM people in quitting smoking. Attention should be paid to messaging about smoking warnings because not all messages are perceived as equally effective by sexual minorities when compared with heterosexual people. Patients should be encouraged to check with community or online resources for smoking cessation programs and encourage participation in SGM tailored programs, if available.

Azagba S et al. Cigarette smoking, e-cigarette use, and sexual identity among high school students in the USA. *Eur J Pediatr.* 2019;178:1343. [PMID: 31292730]

Berger I et al. Smoking cessation programs for lesbian, gay, bisexual, transgender, and intersex people: a content-based systematic review. *Nicotine Tob Res.* 2017;19:1408. [PMID: 27613909]

► Body Weight

Most studies suggest higher prevalence of obesity and overweight in lesbians and bisexual women compared with heterosexual women. The prevalence of obesity may not be uniform across racial and ethnic groups, and sexual minority women of color may experience higher rates of obesity compared with White sexual minority women, although data are mixed. The reason for this difference is likely multifactorial and complex. Obesity and overweight may start at a young age in lesbian and bisexual youth, and they may conceptualize their weight differently than heterosexual peers.

A 2019 study found significant differences between bisexual women, lesbians, and heterosexual adults in body perception and ideals. Studies of physical activity have found that while there may be greater physical activity and fitness among some sexual minority women, sedentary time is also increased in some. The United States Nurses Health Study II found higher diet quality among lesbian and bisexual

► Smoking

Cigarette smoking is more common among lesbian and bisexual women than in heterosexual women. While estimates vary, the National Adult Tobacco Survey noted 22% of lesbian women and 32% of bisexual women smoke compared with 13% of heterosexual women. Studies from Australia and Ireland also show consistently higher smoking rates for sexual minorities. The tobacco industry's well-documented targeted marketing to SGM groups and the use of cigarette smoking to decrease social stress are contributing factors. A 2019 study found that early initiation of smoking (before age 15) accounts for 22–29% of the disparities in adult smoking rates, and rates of cigarette smoking and e-cigarette use in sexual minority high school students are consistently higher than heterosexual peers, particularly for bisexual youth. Protective factors against

women compared with heterosexual women. Psychosocial stress also plays a role. Bullying has been associated with high levels of unhealthy weight control behavior in sexual minority youth. Lifetime trauma exposure has been associated with obesity in sexual minority women, and a 2019 study of lesbian women showed an association between unhealthy eating patterns (binge eating, disordered eating and hazardous alcohol use, disordered eating and high exercise) with higher rates of general discrimination, sexual minority stress, social anxiety, negative affect, and lower social support.

Focus groups have identified themes related to weight for lesbian and bisexual women: aging, physical and mental health status, community norms, subgroup differences, family and partner support, and awareness and tracking of diet and physical activity. Participants expressed feeling unprepared for age-related changes to their health and voiced interest in interventions addressing these issues. Findings from focus groups included (1) a preference for interventions focusing on promoting health and full life participation rather than on weight loss only, (2) cultural norms within the lesbian community that were accepting of larger body types, (3) an increased awareness in older age that the larger body size may exacerbate chronic health problems such as knee pain, and (4) the importance of social support and group structures in initiating and maintaining healthy behaviors.

Henn AT et al. Body image as well as eating disorder and body dysmorphic disorder symptoms in heterosexual, homosexual, and bisexual women. *Front Psychiatry*. 2019;10:531. [PMID: 31427996]

Ingraham N. Perceptions of body size and health among older queer women of size following participation in a health programme. *Cult Health Sex*. 2019;21:636. [PMID: 30295146]

Mason TB et al. Clustered patterns of behavioral and health-related variables among young lesbian women. *Behav Ther*. 2019;50:683. [PMID: 31208679]

Pistella J et al. The role of peer victimization, sexual identity, and gender on unhealthy weight control behaviors in a representative sample of Texas youth. *Int J Eat Disord*. 2019;52:597. [PMID: 30805974]

diabetes, efforts to prevent obesity may also decrease disparities in diabetes and prediabetes.

Corliss HL et al. Risk of type 2 diabetes among lesbian, bisexual, and heterosexual women: findings from the Nurses' Health Study II. *Diabetes Care*. 2018;41:1448. [PMID: 29720541]

Liu H et al. Sexual orientation and diabetes during the transition to adulthood. *LGBT Health*. 2019;6:227. [PMID: 31170023]

Newlin K et al. Prevalence of obesity, prediabetes and diabetes in sexual minority women of diverse races/ethnicities: findings from the 2014–2015 BRFSS surveys. *Diabetes Educ*. 2018; 44:348. [PMID: 29808733]

► Prevention of Pulmonary Disease

Pulmonary disease has not been rigorously studied in lesbian or bisexual women; most of the data come from studies of asthma, which generally find higher rates in sexual minority women compared with heterosexual women. Older lesbian women have a higher prevalence of lifetime and current asthma, even when statistical models are used to correct for current and past smoking and obesity. Increasingly, as this field of research matures, other findings of mediators on pulmonary health may help elucidate possible causative factors of pulmonary health. For example, one study of SGM persons found an association between shorter duration of sleep and outcomes, such as COPD prevalence. Further research is needed in this field, particularly considering disparate rates of smoking in sexual minority women that may predispose to pulmonary disease.

Cabrera-Serrano A et al. Tobacco use and associated health conditions and risk factors in the lesbian, gay, bisexual, transgender, and transsexual populations of Puerto Rico, 2013–2015. *PR Health Sci J*. 2019;38:46. [PMID: 30924915]

Fredriksen-Goldsen KI et al. Chronic health conditions and key health indicators among lesbian, gay, and bisexual older US adults, 2013–2014. *Am J Public Health*. 2017;107:1332. [PMID: 28700299]

Veldhuis CB et al. Asthma status and risk among lesbian, gay, and bisexual adults in the United States: a scoping review. *Ann Allergy Asthma Immunol*. 2019;122:535. [PMID: 30721759]

Veliz P et al. LDCT lung cancer screening eligibility and use of CT scans for lung cancer among sexual minorities. *Cancer Epidemiol*. 2019;60:51. [PMID: 30909153]

► Prevention of Diabetes

There are limited studies examining diabetes and prediabetes in sexual minority women and results are conflicting. In the Nurse's Health Study II, for example, lesbian and bisexual women had a 27% higher risk of developing type 2 diabetes than heterosexual women; however, this association was mediated by BMI. Data from the Behavioral Risk Factor Surveillance System (2014–2015) showed reduced odds of diabetes in bisexual women and no difference in lesbians compared with heterosexual women, although these findings differed by race/ethnicity. In this study, Hispanic lesbian women had higher odds of diabetes compared with White lesbian women (AOR 3.76) but not Hispanic heterosexual women; Black bisexual women had higher odds of diabetes compared with White bisexual women (AOR 2.03) but Black lesbian and bisexual women had lower odds of diabetes compared with Black heterosexual women. Given the association between obesity and

► Prevention of Sexually Transmitted Infections

STIs occur in lesbian and bisexual women, but little population-based data are available to delineate precise risks. Asking about sexual *behaviors* in addition to sexual *identity* is key to identifying STI risk and advising appropriate testing, since risk may vary by specific sexual practice (eg, digital-vaginal, vaginal-vaginal, digital-anal, oral-vaginal, oral-anal contact) and the specific pathogen. Often data are mixed and inconsistent with respect to whether sources speak to infection risk by identity group or behavior. Delineating behavior-based risk and identity-based risk are important for research, assessments, and interventions. The CDC has found that women who have sex with women (WSW is identity-based) have diverse sexual practices (sexual practices are behavior-based); the CDC also

noted that use of barrier protection in examined studies (eg, use of gloves, dental dams) was ubiquitously low.

Chlamydial infections were higher in 14- to 24-year-old women who reported same-sex behavior when attending family planning clinics in the US Pacific Northwest compared to women who reported exclusively heterosexual behavior. Possible explanations for this observation include differences in these groups' use of reproductive health care services, infrequent use of barrier methods to prevent STI transmission with female partners, trends toward higher-risk behaviors, and different social network characteristics. Regardless of sexual orientation, the CDC recommends annual *Chlamydia trachomatis* (and *Neisseria gonorrhoeae*) screening from the age of first sexual activity to the age of 25 years for all women.

It is important to ask lesbian and bisexual women about specific sexual practices, as some practices may carry a higher risk of STIs than others, although there has been little research on sexual practices and the risk of STIs in this population. Thus, inferences are drawn from heterosexual prevention of these infections. "Safer Sex Kits" have occasionally been distributed to WSW and women who have sex with women and men (WSWM) to decrease the risk of STIs, but intervention effectiveness has not been studied. These kits often include dental dams to prevent transmission of bacteria and viruses from oral sex, but the efficacy of dental dams for this function has not been studied. Female latex condoms and latex gloves may provide better protection against infectious transmission from oral sex since latex has been studied as a barrier for prevention of HIV and other STIs. Exchange of blood should be avoided as much as possible, especially in HIV-discordant lesbian couples, since viral genotype analysis has confirmed that HIV can be transmitted sexually between women. The clinician should encourage both partners in new lesbian couples to have comprehensive STI and HIV screening prior to sexual contact and recommend barrier protection for 6 months until the couple is again screened to verify that their HIV status is still negative. If the couple is consistently monogamous and HIV and other STI testing are negative, barrier precautions do not need to be continued. However, lesbian and bisexual women may not follow this advice, since many feel they are at low risk for HIV, which may be correct, but data are lacking. About 20–50% of lesbian women use sexual aids (eg, vibrators, dildos, or other sexual toys); these should not be shared with partners and should be cleaned after use. The human papillomavirus (HPV) can remain on these sexual aids for up to 24 hours after use, even after standard cleaning. Some lesbian and bisexual women are sex workers or have had sexual relationships with high-risk male sexual partners (sometimes gay male friends) and are at increased risk for STIs. CDC guidelines recommend that all women should be tested once in their lifetime for HIV, with testing repeated according to risk factors.

The herpes simplex virus (HSV) can be transmitted sexually between women. The same precautions regarding the transmission of HSV should be provided to lesbian, bisexual, and heterosexual women; there should be no sexual contact during any prodromal symptoms that

may precede a genital herpes outbreak or during the blister stage of the outbreak. Suppression of lesions can usually be accomplished with antiviral medications, such as acyclovir or valacyclovir, if the lesions are recurrent (see Chapter 6).

There is evidence of HPV transmission between female sexual partners. Certain strains of HPV are causally related to many precancerous and cancerous lesions, including cervical dysplasia and cervical cancer (see Chapter 18). Ten percent of lesbian women have never had sex with men, yet cervical dysplasia and cervical cancer develop in some of these women. All women (including lesbian women) need cervical cancer screening, which may include Papanicolaou smears, high-risk HPV strain testing, or both, according to timetables and risk factors provided by professional society guidelines. The rate of HPV vaccination in Black lesbian women was very low in one study; the OR for HPV vaccination was 0.16 for Black lesbian women compared to White heterosexual women, and 0.35 for White lesbian women compared to White heterosexual women. Bisexual women are vaccinated more frequently than either lesbian or heterosexual women. However, the overall HPV vaccination rate is low in adult women regardless of sexual orientation, so improvement in all groups should be the goal. Administration of the HPV vaccine is critical to the prevention of cervical cancer; the CDC recommends HPV vaccination for all persons through age 26 years; for unvaccinated adults ages 27 through 45 years, shared decision making is recommended. Despite recommendations that cervical cancer screening, usually Papanicolaou testing, be performed regardless of sexual orientation, Papanicolaou testing varies according to identity irrespective of behavior and some studies modify screening according to identity and behavior. In a national probability sample of who underwent Papanicolaou testing, WSWM had the same odds of testing as WSM only, whereas women with lifetime female partners had lower odds of testing. Those who identified as bisexual also had lower odds of testing.

Trichomonas vaginalis can be transmitted easily between female sexual partners. One study of women attending an STI clinic in the United States noted that *T vaginalis* was the most common curable STI found in this population with a prevalence of 17% in WSW and 24% in WSWM.

Bacterial vaginosis is common among women and, according to the CDC, even more common among WSW. It is unknown whether bacterial vaginosis can be transmitted between women. A study from Australia found a 27% prevalence of bacterial vaginosis in women and their female partners; risk factors for bacterial vaginosis were four or more lifetime female sexual partners, a female partner with bacterial vaginosis symptoms, and smoking at least 30 cigarettes weekly. Routine screening for bacterial vaginosis, though, is not currently recommended and testing should be based on symptoms. One approach for a WSW who has symptomatic bacterial vaginosis is to treat her and not her female sexual partner. If symptoms recur, her female sexual partner(s) should be evaluated and treated with consideration of re-treating the index woman. This strategy may also be used for treatment of recurrent or hard to treat vulvovaginal candidiasis, which technically is

not considered to be sexually transmitted, but anecdotally, improvement has occurred with treatment of the index patient and female partner.

Various strategies for making reproductive and sexual health clinics and providers more amenable to serving SGM people were studied by a group in the United States, but the findings (such as ensuring counseling involves inclusive safe sex discussions that are relevant to SGM people) have broad face validity and relevance for other regional and medical focus settings as well.

Agénor M et al. Human papillomavirus vaccination initiation among sexual orientation identity and racial/ethnic subgroups of black and white U.S. women and girls: an intersectional analysis. *J Womens Health (Larchmt)*. 2018;27:1349. [PMID: 29957092]

Everett BG et al. Do sexual minorities receive appropriate sexual and reproductive health care and counseling? *J Womens Health (Larchmt)*. 2019;28:53. [PMID: 30372369]

McCune KC et al. Clinical care of lesbian and bisexual women for the obstetrician gynecologist. *Clin Obstet Gynecol*. 2018;61:663. [PMID: 30285974]

Wingo E et al. Reproductive health care priorities and barriers to effective care for LGBTQ people assigned female at birth: a qualitative study. *Womens Health Issues*. 2018;28:350. [PMID: 29661698]

Israel T et al. Development and evaluation of training for rural LGBTQ mental health peer advocates. *Rural Ment Health*. 2016;40:40. [PMID: 27516816]

Schuler MS et al. Substance use disparities at the intersection of sexual identity and race/ethnicity: results from the 2015–2018 national survey on drug use and health. *LGBT Health*. 2020;7:283. [PMID: 32543315]

Watson RJ et al. Associations between community-level LGBTQ-supportive factors and substance use among sexual minority adolescents. *LGBT Health*. 2020;7:82. [PMID: 31985327]

► Cancer Risk, Prevention, & Treatment

Little is known about the incidence and prevalence of various cancers in lesbian and bisexual women, since sexual orientation has not been routinely included in cancer screening programs and cancer registries. However, some data suggest that sexual minority women may be at a higher risk for cancer-related mortality than heterosexual counterparts. Investigators from the Women's Health Study compared sexual minority veterans and civilians to their heterosexual counterparts and found that sexual minority women veterans had a higher risk of cancer-specific mortality. A population-based study from the United Kingdom found higher rates of cancer among gay and bisexual men but no difference in cancer diagnoses between lesbian and bisexual women and their heterosexual counterparts except for a higher rates of oropharyngeal cancer (OR 3.2). Conversely, the National Health Interview Survey found bisexual women over age 65 were 7.6% more likely to be diagnosed with cancer than a heterosexual woman of the same age, but the difference was not seen between lesbian and heterosexual women. Additionally, further analyses of US National Health Interview Survey showed that lesbian and bisexual women have higher prevalence of cancer risk factors, such as tobacco use, underscoring the need for vigilant screening. Since lesbian and bisexual women have barriers to accessing health care and may not see a clinician on an annual basis, any visit to a health care provider is an opportunity to check on cancer screening status (eg, colonoscopy, mammography, cervical cancer screening). There is also recognition that upon receiving a cancer diagnosis, SGM people face challenges in receiving equitable care throughout the cancer care continuum and may experience cancer differently and have different needs during their care; heterosexual and sexual minority cancer survivors in the UK reported receiving different care. The US National Cancer Care Network Guidelines do not address how SGM status should be considered in site-specific guidelines. One qualitative study with SGM breast cancer survivors underscored the challenges of disclosing sexual orientation during cancer care and the importance of provider recognition that varying social networks are critical to positive experiences of care provision. The 2017 American Society for Clinical Oncology position statement recommends five action steps to enhance SGM cancer care and reduce disparities: (1) patient education and support, (2) workforce development and diversity, (3) quality improvement strategies, (4) policy solutions, and (5) research strategies. All providers need to consider whether their prevention, screening, diagnostic, treatment, and palliative approaches will be equitably experienced by lesbian and bisexual women.

► Prevention of Substance Use

Substance use is higher in lesbian and bisexual women compared to heterosexual women and is especially well-documented for cigarette smoking and alcohol use. A secondary analysis of alcohol, tobacco, and other drug use among lesbian and bisexual women in the American College Health Association's National College Health Assessment revealed that bisexual women had greater odds of using alcohol, tobacco, and marijuana than heterosexual women and lesbian women. Lesbian women had greater odds of using tobacco, marijuana, sedatives, hallucinogens, and other illicit drugs and misusing prescription drugs than heterosexual women. This increased rate of substance use persists for bisexual women over the age of 25 but decreases for lesbian women at that time.

Multiple interventions have been initiated to decrease alcohol and other substance use in lesbian and bisexual female youth. In Canada, there were significant lower odds. A 2020 study showed that greater LGBT supportive factors in a community (eg, PRIDE events) correlate with lower lifetime odds of marijuana use and smoking for girls. Recommendations for improving substance use treatment for sexual minority persons include providing interventionists with training in SGM cultural sensitivity. Another approach studied in the rural United States looked at training and deploying SGM peer-advocates to support mental health and substance use and "bridge the gap in culturally competent care." Sexual minority women, compared to heterosexual women, with lifetime alcohol use disorders are at heightened risk for concomitant psychiatric and drug use disorders, underscoring the need for substance abuse programs to provide access to individual counseling with mental health professionals.

Gonzales G et al. Cancer diagnoses among lesbian, gay, and bisexual adults: results from the 2013–2016 National Health Interview Survey. *Cancer Causes Control.* 2018;29:845. [PMID: 30043193]

Hudson J et al. Sexual and gender minority issues across NCCN Guidelines: results from a national survey. *J Natl Compr Canc Netw.* 2017;15:1379. [PMID: 29118229]

Obedin-Maliver J. Time to change: supporting sexual and gender minority people—an underserved, understudied cancer risk population. *J Natl Compr Canc Netw.* 2017;15:1305. [PMID: 29118223]

Saunders CL et al. Associations between sexual orientation and overall and site-specific diagnosis of cancer: evidence from two national patient surveys in England. *J Clin Oncol.* 2017; 35:3654. [PMID: 2894550]

A. Breast Cancer

The literature has been mixed on whether lesbian and bisexual women have a slight increased risk of breast cancer compared to heterosexual women. A 2013 systemic review found the few prevalence studies of breast cancer in lesbians unreliable; however, lesbian women do have an increased prevalence of risk factors predisposing to breast cancer, including nulliparity (and decreased breastfeeding), alcohol use, obesity, and cigarette smoking. Vulnerability to inadequate screening, the development of cancer, or delayed diagnosis may further correlate with certain experiences such as a masculine gender presentation and practices like chest binding, as one study in China found. The literature is also inconsistent regarding the rate of mammography screening in lesbian women; however, a study done in Massachusetts showed that bisexual women were less likely than heterosexual women and lesbian women to adhere to mammography screening guidelines. Lesbian and bisexual women who have breast cancer may not want reconstruction at the same rate as heterosexual women and often find that breast cancer support groups focus on issues for heterosexual women (such as attractiveness to a male partner). Resilience and recovery factors vary in some ways between heterosexual and sexual minority women.

Bazzi AR et al. Resilience among breast cancer survivors of different sexual orientations. *LGBT Health.* 2018;5:295. [PMID: 29878863]

Liu PL et al. Breast health, risk factors, and cancer screening among lesbian, bisexual, and queer/questioning women in China. *Health Care Women Int.* 2019;1. [PMID: 30730783]

B. Cervical Cancer

Primary prevention of cervical cancer is essential. All persons between the ages of 9 and 45 years (routine recommended age is 11 to 12 years old) should receive the HPV vaccine series. HPV can be transmitted sexually between lesbian or heterosexual partners. Cervical cancer screening, with Papanicolaou smears, primary HPV testing, or both, should be part of lesbian and bisexual women's health care at the same intervals as for heterosexual women according to national and international guidelines. Lesbian and bisexual women, however, receive Papanicolaou smears at a lower rate than sexually active heterosexual women, in part because many of the Papanicolaou smears

are done in reproductive health clinics; lesbians who are not interested in becoming pregnant or avoiding pregnancy may not access these clinical sites. In addition, some lesbian patients as well as their health care providers mistakenly think that lesbian women do not need Papanicolaou smears. *All lesbian and bisexual women need cervical cancer screening starting at the age of 21, consistent with recommendations for cervical cancer screening for all women.*

C. Lung Cancer

Compared to heterosexual women, the rate of lung cancer is likely higher in lesbian and bisexual women due to their increased rate of cigarette smoking. The incidence and prevalence of lung cancer, however, have not been determined in this sexual minority population. Nonetheless, gay men and lesbian women with significant use of cigarettes are at increased risk for lung cancer and are underscreened for early lung cancer detection with the use of low-dose helical computed tomography.

D. Endometrial and Ovarian Cancer

Endometrial and ovarian cancers are increased among those with nulliparity, which is more likely in sexual minority women. Obesity, a known risk factor for both cancers, appears to be more prevalent among sexual minority women. Conversely, the use of oral contraceptives, which is protective against the development of both of these cancers, is lower in lesbian women than in heterosexual women. Vigilance toward and education about presenting signs and symptoms (eg, postmenopausal bleeding, early satiety, unintended weight loss) are important to detect cancers as early as possible. Neither incidence nor prevalence of endometrial or ovarian cancer has been determined in this sexual minority population.

Bazzi AR et al. Adherence to mammography screening guidelines among transgender persons and sexual minority women. *Am J Public Health.* 2015;105:2356. [PMID: 26378843]

Lunn MR et al. Sociodemographic characteristics and health outcomes among lesbian, gay, and bisexual U.S. adults using Healthy People 2020 leading health indicators. *LGBT Health.* 2017;4:283. [PMID: 28727950]

Simoni JM et al. Disparities in physical health conditions among lesbian and bisexual women: a systematic review of population-based studies. *J Homosex.* 2017;64:32. [PMID: 27074088]

► Prevention of Violence

Compared to heterosexual women, lesbian and bisexual women have higher exposures to violence throughout their lifetimes. Lifetime prevalence of sexual assault may be as high as 85%. A 2019 study concluded that sexual orientation clearly plays a role in victimization when they found that compared with heterosexual women, bisexual women had 3.7 times the odds of initial victimization and 7.3 times the odds of repeat victimization, and lesbian women had 3.2 times the odds of repeat victimization even after controlling for other sociodemographic factors. In a study of four countries in southern Africa, nearly one-third of lesbian and bisexual women experienced forced sex and assault including "corrective rape" by men as an attempt to

change the women's sexual orientation. In a study from Brazil, qualitative interviews were done of youth coming out to their families: The family reactions were often violent, with persecution and even expulsion from the home, which impacted the youth's health and quality of life.

The CDC reports that 61% of bisexual women and 44% of lesbian women experience rape, physical violence, and stalking by an intimate partner. These rates are higher than similar trauma in heterosexual women (35%). Additionally, approximately 20% of bisexual women compared with 10% of heterosexual women have been raped by an intimate partner in their lifetimes. The rate of stalking experienced by bisexual women is twice that of heterosexual women and a higher percentage of bisexual women report being afraid of an intimate partner. A study of United States armed services veterans found that compared to heterosexual women veterans, lesbian, bisexual, and queer women veterans were twice as likely to report emotional mistreatment and physical intimate partner violence and three times as likely to report sexual intimate partner violence. Despite alarming rates for women of any identity, lesbian and bisexual women survivors of sexual assault and interpersonal violence may experience unique difficulties when seeking assistance. These problems include a limited understanding of interpersonal violence in the relationships of lesbian and bisexual women, stigma, and systemic inequities (such as shelters unwelcome to this population, perpetrating partners being allowed into the same shelters as the survivor of the domestic violence, "outing" someone as a psychological threat, and staff lacking cultural sensitivity and appropriate training in working with lesbian and bisexual women). Barriers to preventing SGM violence include stigma, systemic discrimination, and a lack of understanding of SGM intimate partner violence.

Community violence is experienced more frequently by SGM persons. In-depth interviews of 19 Flemish sexual minority victims of violence revealed the use of four coping strategies: (1) avoidance, (2) assertiveness and confrontation, (3) cognitive change, and (4) social support. Applying these coping skills and actively attaching meaning to negative experiences helped victims of anti-SGM violence overcome fear, embarrassment, or depressive feelings. The presence of a supportive network was important in facilitating the positive outcomes.

Braga IF et al. Family violence against gay and lesbian adolescents and young people: a qualitative study. *Rev Bras Enferm.* 2018;71:1220. [PMID: 29972518]

Canan SN et al. Differences in lesbian, bisexual, and heterosexual women's experiences of sexual assault and rape in a national U.S. sample. *J Interpers Violence.* 2019;88:6260519863725. [PMID: 31347442]

Dardis CM et al. Intimate partner violence among women veterans by sexual orientation. *Women Health.* 2017;57:775. [PMID: 27322372]

and cardiovascular risk, have been attributed to minority stress. Therefore, rather than identifying mental health problems as synonymous with a sexual minority identity or stemming from in-born association with minority sexual orientation, minority stress causes mental health challenges that stem from societal discrimination and stigma borne by individuals with minority identities (and behaviors). An examination of lesbian and bisexual women veterans from the United States Behavioral Risk Factor Surveillance System found that sexual minority women veterans were three times more likely than heterosexual women to experience "mental distress." Mortality risk from suicide is also elevated among women with same-sex partners. In the United States National Epidemiologic Survey on Alcohol and Related Conditions-III, bisexual women had greater rates of specific psychiatric disorders than lesbians or heterosexual women. Resilience factors that are protective for mental distress and poorer mental health among lesbian, gay, bisexual, queer and questioning youth and adults in Israel included family support as well as other community-level factors, such as friends' support, SGM connectedness, and having a steady partner. How parents react to an adolescent's "coming out" has a profound effect on their child's health outcomes. For those adolescents whose parents were supportive, there was less homelessness, depression, substance use, and unprotected sex. Interventions for building resilience can be important in achieving a reduction in anxiety and depression. There is some evidence that online friends can serve as a buffer and social support, especially for SGM youth, although in-person social support appears to be more protective against victimization. However, social media can also be a place where SGM youth experience bullying.

There is evidence that being in a legally recognized same-sex relationship, particularly in marriage, diminishes mental health differences between heterosexual and lesbian, gay, and bisexual persons. In contrast, psychiatric disorders increased among lesbian, gay, and bisexual persons who lived in states in the United States that enacted constitutional amendments to ban same-sex marriage compared to states that did not. One study examined the mental health of individuals living in states before (wave 1, 2001–2002) and after (wave 2, 2004–2005) the enactment of same-sex marriage bans in 2004–2005. Among LGB respondents living in states that enacted the marriage bans, the National Epidemiologic Survey on Alcohol and Related Conditions (N = 34,653) revealed that there was a significantly increased prevalence of any mood disorder (36% increase), generalized anxiety disorder (248% increase), any alcohol use disorder (42% increase), and psychiatric comorbidity (36.3%) between wave 1 and wave 2 of the survey, suggesting that living in sociopolitical environments that do not legally recognize same-sex relationships can have deleterious effects on mental health.

Mental health inequities among bisexual and lesbian women are well documented. Compared to heterosexual women, bisexual and lesbian women are more likely to report lifetime depressive disorders, with bisexual women often faring the worst on mental health outcome. Risk factors for depression, such as victimization in childhood and

► Prevention of Mental Disorders

Lesbians and bisexual women have an increased risk of depression. Many of the health disparities and health risks faced by lesbians and bisexual women, such as depression

adulthood, are more prevalent among bisexual women. One Chicago Health and Life Experiences study (an 18-year, community-based longitudinal study of sexual minority women's health) compared Black bisexual and Black lesbian women with White lesbian women. The study found reports of victimization were higher in Black bisexual and Black lesbian women but the odds of depression were significantly lower than in White lesbian women.

Internalized homophobia was significantly associated with depressive symptoms in a study in South Korea of LGB people. Only 22% had "come out" to their mother, and 11% to their father. Since the early 2000s, suicide rates in South Korea are among the highest of the Organization for Economic Co-operation and Development nations. The conclusion was that mental health interventions were needed for LGB adults who have high levels of internalized homophobia, as well as greater efforts are needed to enact protective legislation for sexual minority individuals in South Korea.

Bostwick WB et al. Depression and victimization in a community sample of bisexual and lesbian women: an intersectional approach. *Arch Sex Behav*. 2019;48:131. [PMID: 29968037]
 Jackman K et al. Nonsuicidal self-injury among lesbian, gay, bisexual and transgender populations: an integrative review. *J Clin Nurs*. 2016;25:3438. [PMID: 27272643]

Kerridge BT et al. Prevalence, sociodemographic correlates and DSM-5 substance use disorders and other psychiatric disorders among sexual minorities in the United States. *Drug Alcohol Depend*. 2017;170:82. [PMID: 27883948]

Lee H et al. Internalized homophobia, depressive symptoms, and suicidal ideation among lesbian, gay and bisexual adults in South Korea: an age-stratified analysis. *LGBT Health* 2019;8:393. [PMID: 31746660]

McDermott E et al. The social determinants of lesbian, gay, bisexual and transgender youth suicidality in England: a mixed methods study. *J Public Health (Oxf)*. 2018;40:e244. [PMID: 29045707]

Schulman JK et al. Mental health in sexual minority and transgender women. *Med Clin North Am*. 2019;103:723. [PMID: 31078203]

sexual orientation used in surveys and the possibility that some survey respondents do not disclose gay or bisexual orientations because of concerns about discrimination. Nevertheless, based on available data, it is estimated that at least 2.2% of American adult men identify as gay, and an additional 1.4% of men identify as bisexual. The proportion of men who engage in sex with other men or experience sexual attraction to other men is estimated to be higher, with 7.3% and 6.2% of adult men reporting some same-sex attraction and sexual behavior, respectively, in one national survey.

► Health Disparities

Gay, bisexual, and other MSM face health disparities stemming from the biologic aspects of their sexual behavior and/or from minority stress. Because of these disparities, MSM have been identified as a priority population for health-related research and improvement in health care by both the National Academy of Medicine and the federal government's Healthy People initiative. These health disparities are exacerbated if young MSM have experienced early life traumatic events, such as sexual abuse or familial rejection.

Office of Disease Prevention and Health Promotion (ODPHP). *Healthy People 2020: lesbian, gay, bisexual, and transgender health*. 2016. <https://www.healthypeople.gov/2020/topics-objectives/topic/lesbian-gay-bisexual-and-transgender-health>

A. HIV and Other STIs

MSM account for approximately 70% of all new HIV infections in the United States, despite representing a small proportion (less than 10% by any metric) of the country's male population. The high burden of HIV infection among MSM stems in part from the efficient transmission of the virus through receptive anal intercourse, which confers a higher risk of HIV infection than other sexual activities, such as penile-vaginal and oral intercourse. Role versatility can also uniquely potentiate HIV spread among MSM, since the same person can acquire HIV via receptive intercourse and then transmit by engaging in insertive anal intercourse with HIV-uninfected partners. The origin of disparate HIV rates between MSM and other populations is not solely biologic in origin, however, as societal stigma and psychosocial problems also contribute to sexual risk behavior among MSM. MSM of color face an increased risk of HIV; the CDC estimates that the lifetime risk of HIV infection is 1 in 2 for African American MSM and 1 in 4 for Latino MSM compared to 1 in 11 for White MSM. Racial and ethnic disparities in HIV infections among MSM do not appear to be due to differences in sexual behavior or substance use but rather factors such as lack of access to medical care, lower rates of recent HIV testing among non-White MSM, and assortative mixing (ie, being more likely to have sex with partners from one's own racial or ethnic group).

Beyond HIV, some STIs are more common among MSM. In 2018, 64% of primary and secondary syphilis diagnoses occurred in MSM or men who have sex with

HEALTH CARE FOR GAY & BISEXUAL MEN

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This section is devoted to the primary care of cisgender (that is, non-transgender) gay, bisexual, and other MSM regardless of their sexual identity. Most health-related research that focuses on MSM categorizes men based on their sexual behavior as MSM, rather than their self-reported identification as gay, bisexual, or other identities. Although sexual identity is not always congruent with sexual behavior, identity is important to recognize in order to optimize health and health care, especially when there is a difference on the basis of sexual identity (for example, gay- vs bisexual-identified men).

► Demographics

The size of the MSM population in the United States is not known with certainty due to variability in the definition of

both men and women. Syphilis is associated with a high risk of subsequent HIV acquisition in MSM and may serve as a marker for individuals who could benefit from intensive HIV prevention efforts, such as the initiation of PrEP. Increased cases of ocular syphilis, occasionally resulting in blindness, have been reported, with a majority of cases occurring in MSM. The incidence of gonorrhea among MSM exceeds that among men who have sex with women (MSW) and has increased. MSM also are more likely than MSW to be infected with antibiotic-resistant gonorrhea. Most gonococcal infections in MSM occur at extragenital sites (ie, the pharynx or the rectum) where they may be asymptomatic, underscoring the importance of eliciting a comprehensive sexual history, including an inventory of potential anatomic exposures, in order to provide optimal STI screening for MSM.

MSM face increased risks of viral hepatitis. Outbreaks of hepatitis A infection have been documented in MSM, likely due to anal sexual contact, including oral-anal exposure ("rimming") as well as insertive and receptive practices. Likewise, hepatitis B is more common among MSM than the general population; approximately 20% of MSM have evidence of either current or prior infection with hepatitis B by age 30. This highlights the importance of universal hepatitis A and B vaccination for young MSM, preferably prior to the initiation of sexual contact. Finally, hepatitis C infection has been identified as increasingly prevalent among HIV-infected and high-risk HIV-uninfected MSM; although hepatitis C is generally not efficiently transmitted via sexual contact, it is associated with condomless receptive anal sex, group sex, manual insertion of fingers into the rectum ("fisting"), and recent STIs, which make the rectal mucosa more susceptible to hepatitis C acquisition and transmission.

HPV infection, which can cause anogenital warts, anal dysplasia, and anal cancer, is more common among MSM than MSW. A meta-analysis estimated the prevalence of the oncogenic HPV type 16 in the anal canal to be 35.4% among HIV-positive MSM and 12.5% among HIV-negative MSM. Correspondingly, anal cancer incidence is higher among HIV-positive versus HIV-negative MSM. Studies are underway to determine the optimal frequency of screening for anal cellular atypia and follow-up high resolution anoscopy for sexually active MSM.

Enteric infections may be sexually transmitted among MSM engaging in anal sexual contact, especially oral-anal sexual contact, and should be considered in the differential diagnosis of gastrointestinal complaints. These infections include giardiasis, amebiasis, and shigellosis. In addition, *Shigella* infections are more likely to be antibiotic resistant among MSM than among other individuals.

Clusters of meningococcal disease among MSM in the United States and Europe have also been reported, particularly those frequenting sexualized environments, including saunas and bathhouses, prompting some jurisdictions to recommend meningococcal vaccination for high-risk MSM. Intimate contact with multiple partners has been identified as a risk factor for infection in some of these outbreaks.

Centers for Disease Control and Prevention (CDC). HIV among African American gay and bisexual men. 2018. <https://www.cdc.gov/hiv/group/msm/bmsm.html>

Centers for Disease Control and Prevention (CDC). HIV among gay and bisexual men. 2017. <https://www.cdc.gov/hiv/group/msm/index.html>

Nanduri S et al. Outbreak of serogroup C meningococcal disease primarily affecting men who have sex with men—Southern California, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:939. [PMID: 27606798]

Nyitray AG et al. Incidence, duration, persistence, and factors associated with high-risk anal human papillomavirus persistence among HIV-negative men who have sex with men: a multinational study. Clin Infect Dis. 2016;62:1367. [PMID: 26962079]

B. Behavioral Health

Likely due to minority stress (ie, growing up in non-affirming societies), MSM experience mental health disorders more commonly than other men. Whether defined by self-reported identity as gay or bisexual or behaviorally by report of sexual activity with other men, MSM have a higher lifetime prevalence of depression and anxiety disorders than men who identify as heterosexual and/or who report sexual activity only with women. Behaviorally bisexual men experience a higher burden of both depression and anxiety disorders, compared to men who engage in only homosexual behavior, in part because bisexual men may not have access to defined communities of choice, like self-identified gay men. The increased prevalence of mental health disorders among behaviorally bisexual men may also stem from dual stigmatization by both the heterosexual and gay male communities, as well as internalized stigma. Among MSM overall, anti-gay violence, community alienation, and dissatisfaction with an idealized body image have all been associated with depression.

C. Substance Use

Compared to men with only female sexual partners, MSM are more likely to report lifetime recreational drug use; they are specifically more likely to have used cocaine, hallucinogens, inhalants, analgesics, and tranquilizers. In addition, men who identify as gay or bisexual are more likely to smoke cigarettes than those who identify as heterosexual. Although it is not clear that MSM are more likely than others to use methamphetamine, methamphetamine use in MSM communities has been linked to increased sexual risk behavior and transmission of hepatitis C, HIV, and other STIs. Consistent with the minority stress model, experiences of discrimination have been independently associated with substance use among MSM.

Hoenigl M et al. Clear links between starting methamphetamine and increasing sexual risk behavior: a cohort study among men who have sex with men. J Acquir Immune Defic Syndr. 2016;71:551. [PMID: 26536321]

► Preventive Care & Clinical Practice Guidelines

Clinicians can help address health disparities affecting MSM by following clinical practice guidelines that pertain

Table 42–1. Clinical practice guidelines pertaining to the care of MSM.

Recommendation	Comments
Immunizations	
Human papillomavirus (quadri- or nonavalent)	Recommended up to age 26 years; the vaccine may be offered to those ages 27–45
Hepatitis A and B	Consider prevaccination serologic testing if the immunization history is uncertain; vaccinate if seronegative
Meningococcal	Recommended by some jurisdictions due to outbreaks of meningococcal disease among MSM
Medications	
Preeexposure prophylaxis for HIV	For MSM at high, ongoing risk of HIV infection (eg, condomless anal sex, recent STI diagnosis, HIV-infected sexual partner)
Postexposure prophylaxis for HIV	Consists of 28 days of antiretroviral medication following a discrete exposure to HIV
Screening Tests	
HIV serology	At least annually, more often if high risk
Syphilis serology	At least annually, more often if high risk
Nucleic acid amplification test for gonorrhea and chlamydia	At least annually, more often if high risk; all potentially exposed sites (oropharynx, urethra, rectum) should be screened, as indicated by the sexual history
Hepatitis C serology	Annually for HIV-infected MSM and HIV-uninfected MSM engaging in behaviors that might expose them to blood (for example, injection drug use or traumatic anal sexual practices)
Anal cytology	For HIV-infected MSM; the appropriateness of anal cytology for HIV-uninfected MSM is under study
Behavioral health (depression, substance use)	At the first clinical encounter, with follow-up screening for those who report behavioral health concerns

MSM, men who have sex with men; STI, sexually transmitted infection.

to this population (Table 42–1). The CDC recommends that sexually active MSM undergo screening for HIV, syphilis, gonorrhea, and chlamydia annually and more often if the risk history warrants more frequent assessment. An HIV antibody-antigen assay is preferred for HIV screening because this test increases the sensitivity for detection of acute or recent HIV infection. Nucleic acid amplification testing (NAAT) provides optimal sensitivity for diagnosis of gonorrhea and chlamydia and can be performed on the oropharynx, rectum, urine, and urethra. MSM should be screened for these infections at any of the aforementioned sites that may have been exposed during sex, regardless of condom use. First-catch urine and urethral specimens for gonorrhea and chlamydia NAAT in men provide comparable accuracy; thus, there is no advantage to the urethral swab for routine screening. Rectal and pharyngeal swabs for NAAT can be self-collected.

The CDC also recommends that MSM be screened for chronic hepatitis B infection at least once in their lives and that they be vaccinated against hepatitis A and B. Annual hepatitis C screening with a hepatitis C antibody test is recommended for HIV-infected MSM due to the elevated incidence of this infection in this population and the availability of well-tolerated, curative therapy. HIV-uninfected MSM engaging in sexual practices such as group sex, fist-fucking, and any other practice that may abrade the rectal mucosa may also benefit from annual HCV screening.

The CDC, United States Preventive Services Task Force, and the World Health Organization recommend **preeexposure prophylaxis** for HIV with the fixed-dose combination of tenofovir disoproxil fumarate–emtricitabine for MSM at high risk for HIV infection. PrEP with tenofovir alafenamide–emtricitabine is also approved by the US FDA for MSM. Individuals at high risk include those who engage in condomless anal sex outside of a monogamous relationship with an HIV-uninfected man; those who have recently been diagnosed with a bacterial STI; and those whose sexual partners are HIV-infected. However, the utility of PrEP is likely low in the latter scenario if the relationship is monogamous, the HIV-uninfected person does not inject drug, and the HIV-infected partner is consistently virologically suppressed on antiretroviral therapy because antiretroviral therapy significantly reduces the likelihood of HIV transmission through sexual contact. PrEP has been shown in randomized controlled trials to prevent HIV infection in MSM and is addressed in more detail in Chapter 31.

Clinicians who care for MSM should also be aware of **postexposure prophylaxis (PEP)**, which consists of antiretrovirals started within 72 hours of a discrete exposure to HIV and taken for 28 days, and either provide PEP themselves or be able to rapidly link patients to PEP care (see Chapter 31).

HPV immunization with the quadrivalent or nonavalent vaccines is recommended for all boys and young men

up to age 26. For unvaccinated adults between the ages of 27 and 45, shared decision-making around HPV vaccination is recommended. The HIV Medicine Association (HIVMA) recommends routinely screening HIV-infected MSM for anal cancer with anal cytology; however, this approach has not yet been proven to be beneficial in any randomized controlled clinical trial. In addition, the optimal screening interval (ages at which to initiate and cease screening) and management of abnormal results are not clearly defined. Patients with abnormal anal cytology are typically referred for high-resolution anoscopy with biopsy. Colonoscopy performed for colon cancer screening is not considered a substitute for anal cytology or high-resolution anoscopy because colonoscopy does not assess for cellular abnormalities in the anal canal. Anal cytology screening of HIV-uninfected MSM is not currently recommended in any national consensus guidelines, although some clinicians perform this screening due to the elevated risk of anal cancer in these men. Large prospective studies are underway in the United States and Australia to attempt to address the questions related to optimal timing of anal HPV screening for MSM.

Finally, clinicians should ensure that MSM are offered preventive care recommended for all individuals, including smoking cessation counseling and pharmacotherapy, screening for depression, and assessment for and counseling about alcohol misuse (see Lesbian and Bisexual Women's Health, above). Some studies have found that behavioral health programs tailored specifically for MSM are more effective in promoting healthy behaviors than those that are not culturally sensitive.

Centers for Disease Control and Prevention (CDC). Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV—United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2016;65:458. [PMID: 27149423]

Reback CJ et al. Development of an evidence-based, gay-specific cognitive behavioral therapy intervention for methamphetamine-abusing gay and bisexual men. *Addict Behav.* 2014; 39:1286. [PMID: 22169619]

TRANSGENDER HEALTH & DISEASE PREVENTION

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Terminology

In everyday language “sex” and “gender” are used interchangeably; however, in the context of transgender people, the meanings differ. **Gender expression** describes the outward manner in which an individual expresses or displays gender, including choices in clothing and hairstyle, speech, and mannerisms. Gender identity and gender expression may differ; for example, a woman (transgender or non-transgender) may have an androgynous appearance, or a man (transgender or non-transgender) may have a feminine form of self-expression. Transgender people may not feel comfortable, or be unable to, outwardly express their internal felt sense of gender due to societal,

work, or family pressures. Transgender people who have a well documented and persistent gender identity that differs from their sex assigned at birth and are experiencing distress as a result of this mismatch, meet the diagnostic criteria for gender dysphoria as described in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5).

For the purposes of this text, “transgender” is inclusive of those who identify with the terms gender non-binary, nonconforming, genderqueer, and transsexual. A non-transgender person may be referred to as cisgender (Latin root *cis* = near/next to), which refers to people whose gender identity and birth sex are the same, ie, non-transgender. Non-binary, gender nonconforming, or genderqueer describes a person whose gender identity differs from that assigned at birth but may be more complex, fluid, multifaceted, or otherwise less clearly defined than purely male or female. Non-binary people may use neutral pronouns such as “they,” “them,” or “their.” The term transsexual is an older term that has fallen out of favor and referred specifically to a transgender person who seeks medical interventions. Other related terms include cross dresser, which describes someone who may wear clothing of the opposite gender without a clear identification with that gender, and drag, which describes cross dressing for performance purposes.

Sexual orientation, which describes sexual attraction and behaviors, is not directly related to gender identity. The sexual orientation of transgender people should be described based on the lived gender; a transfeminine person attracted to other women would be a lesbian, and a transmasculine person attracted to other men would be a gay man.

Transgender people may seek any one of a number of gender affirming medical, surgical, or related interventions. Based on research demonstrating positive effects on multiple psychosocial measures, such interventions are recognized as medically necessary by the World Professional Association for Transgender Health (WPATH), an international, multidisciplinary professional organization that publishes widely recognized standards of care. Not all transgender people seek all interventions, and some may seek none; the current standard of care is to allow each transgender person to seek only those interventions they desire to affirm their own gender identity.

Cahill SR et al. Inclusion of sexual orientation and gender identity in stage 3 meaningful use guidelines: a huge step forward for LGBT health. *LGBT Health.* 2016;3:100. [PMID: 26698386]

Coleman E et al. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7. *Int J Transgenderism.* 2012;13:165.

Deutsch MB et al. Electronic medical records and the transgender patient: recommendations from the World Professional Association for Transgender Health EMR Working Group. *J Am Med Inform Assoc.* 2013;20:700. [PMID: 23631835]

Medical Interventions

Many, but not all, transgender people will seek gender affirming hormone therapy and/or surgery (genitals, chest, or face). Transfeminine persons commonly seek facial hair

removal and may also seek voice feminization training. Hormone therapy allows the acquisition of secondary sex characteristics more aligned with an individual's gender identity. The WPATH Standards of Care recognize that hormone therapy is within the scope of practice for primary care providers. The Standards also permit medical providers to prescribe hormone therapy under an informed consent approach without a mental health assessment if the medical provider feels competent to make the diagnosis of gender dysphoria.

A. Feminizing Hormone Therapy

The goal of feminizing hormone therapy is the development of female secondary sex characteristics and suppression/minimization of male secondary sex characteristics. The general approach of therapy is to obtain physiologic premenopausal female range estrogen and testosterone levels through the combined use of an estrogen with an androgen blocker, and in some cases a progestagen. Clinical endpoints include breast development (often maximum Tanner stage 2/3), reduction of body hair, reduced muscle mass, and female redistribution of body fat.

The most commonly used estrogen is 17-beta estradiol, in pill, patch, or, less commonly, injected form. The choice of route is based to some degree on patient preference (Table 42–2). Transdermal estradiol has a well-established safety profile based on studies in menopausal cisgender women. Injected estradiol is the least studied route and can be associated with both supratherapeutic levels as well as cyclical levels over the dosing interval. Estrogens should be continued after gonadectomy without reduction in dose. There is no direct evidence to guide decision making regarding the discontinuation of estrogen once a patient arrives at a menopausal age, though most experts believe initiating or continuing hormone therapy in transfeminine persons after age 50 is appropriate. Ethynodiol (found in combined oral contraceptives) should be avoided due to thrombogenicity and a lack of need for suppression of ovulation.

The most commonly used anti-androgen is spironolactone, a potassium-sparing diuretic that is frequently used for female hirsutism or adult acne. Spironolactone inhibits both the synthesis of and action of testosterone. In higher doses (100–200 mg orally daily), spironolactone can lead to

Table 42–2. Feminizing hormone therapy.

Hormone Therapy	Dosage			Comments
	Initial, Low ¹	Initial, Typical	Maximum, Typical ²	
Estrogen				
Estradiol oral/sublingual	1 mg/day	2–4 mg/day	8 mg/day	If > 2 mg is recommended, dose should be divided and taken twice daily.
Estradiol transdermal	50 mcg	100 mcg	100–400 mcg	Maximum available single patch dose is 100 mcg. Frequency of change is brand and product dependent. Patients may find that > 2 patches at a time are cumbersome.
Estradiol valerate, intramuscularly ³	< 20 mg every 2 weeks	20 mg every 2 weeks	40 mg every 2 weeks	May divide dose into weekly injections for cyclical symptoms.
Estradiol cypionate, intramuscularly	< 2 mg every 2 weeks	2 mg every 2 weeks	5 mg every 2 weeks	May divide dose into weekly injections for cyclical symptoms.
Progestagen				
Medroxyprogesterone acetate (Provera)	2.5 mg orally each night at bedtime		5–10 mg orally each night at bedtime	
Micronized progesterone			100–200 mg each night at bedtime	
Androgen Blocker				
Spironolactone	25 mg orally daily	50 mg orally twice daily	200 mg orally twice daily	
Finasteride	1 mg orally daily		5 mg orally daily	
Dutasteride			0.5 mg orally daily	

¹Initial low dosing for those who desire (or require due to medical history) a low dose or slow upward titration.

²Maximal effect does not necessarily require maximal dosing, as maximal doses do not necessarily represent a target or ideal dose. Dose increases should be based on patient response and monitored hormone levels.

³Available as standard US Pharmacopia (USP) as well as compounded products.

suppression of androgen levels into the female physiologic range. Common side effects include orthostasis and polyuria. Monitoring should include periodic assessment of kidney function and serum potassium. Other options for those who cannot tolerate spironolactone include a gonadotropin-releasing hormone (GnRH) analog, orchiectomy, or the use of a progestagen. Finasteride and dutasteride (5-alpha-reductase inhibitors) are sometimes used as an alternative; however, they have limited effects. After gonadectomy, anti-androgens can be discontinued.

No studies have been conducted on the role of progestagens in transfeminine persons. Some believe there is benefit to breast development, mood, or libido, and there is no clear evidence to suggest any harm related to progestagen use in transfeminine persons. Progestagens may be an effective anti-androgen, particularly cyproterone acetate, which is used widely outside the United States as the primary androgen blocker in feminizing regimens. If used, progestagens should be initiated after at least several months of estrogen plus anti-androgen.

The primary risk associated with estrogen therapy is venous thromboembolism (VTE). However, when using 17-beta estradiol at physiologic estrogen dosing, the risk is minimal. Prior studies showing 20- to 40-fold increased risk of VTE involved the use of ethinyl estradiol at doses of up to 200 mcg/day and did not control for tobacco use. More recent data found no increased risk of VTE in transfeminine persons using transdermal 17-beta estradiol. Thus, transdermal estradiol is the preferred route for those who smoke or with risk factors for or a personal history of VTE.

- Arnold JD et al. Incidence of venous thromboembolism in transgender women receiving oral estradiol. *J Sex Med.* 2016; 13:1773. [PMID: 27671969]
- Deutsch MB. *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People*, 2nd ed. 2016. <https://transcare.ucsf.edu/guidelines>
- Hembree WC et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102:3869. [PMID: 28945902]
- Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metab.* 2014;99: 4379. [PMID: 25140398]

B. Masculinizing Hormone Therapy

The goal of masculinizing hormone therapy is the development of male secondary sex characteristics, and suppression/minimization of female secondary sex characteristics. The general approach involves the use of one of several forms of parenteral testosterone using an approach similar to that in hypogonadal or agonadal cisgender men (Table 42-3). Blockade of estrogen is not needed.

Testosterone may be injected or applied as a topical gel or patch. Two studies support the use of subcutaneous (rather than intramuscular) injections, which allow the use of a smaller needle. The use of topical testosterone or using a weekly (vs biweekly) injection interval can help maintain even hormone levels in those with cyclical mood symptoms or pelvic cramping. Clinical endpoints include the

development of facial hair, deepening of the voice, clitoral growth, male body fat redistribution and muscle growth, and induction of amenorrhea by 6 months.

Prior concerns of testosterone-induced hepatotoxicity were based on the use of oral methyltestosterone. There is no evidence to support a concern of hepatotoxicity in transmasculine persons using parenteral bio-identical testosterone.

Common side effects of testosterone therapy in transmasculine persons include acne and male pattern baldness, both of which can be approached as in cisgender men. Hemoglobin and hematocrit should be monitored, and if the levels are elevated, consider reducing testosterone dose or changing to a transdermal form or weekly injections to maintain more even levels. It is important to use male reference ranges for hemoglobin and hematocrit due to the erythropoietic effects of testosterone and frequent oligo- or amenorrheic status of transmasculine people. Polycystic ovarian syndrome and obesity have been found to be at an increased prevalence in transmasculine persons prior to beginning testosterone therapy. Testosterone is not contraindicated in the presence of these conditions; instead, related metabolic disorders can be managed concurrently.

Olson J et al. Subcutaneous testosterone: an effective delivery mechanism for masculinizing young transgender men. *LGBT Health.* 2014;1:165. [PMID: 26789709]

C. Monitoring Therapy

Hormone effects should be monitored both by clinical results as well as hormone levels, if available. Patients should be reminded that results may vary and can take up to 5 years to reach maximal effect; supraphysiologic hormone levels are not likely to enhance results but may incur risks. Note that reported laboratory reference range values may differ depending on the sex of registration of the patient; in general, clinicians should use the reference ranges driven by the current hormonal status of the patient. For example, female reference ranges will be included on automated laboratory reports of a transmasculine person taking testosterone while still legally registered as female. The interpreting clinician should use the male reference ranges for any tests run on this patient that have sexually dimorphic reference ranges. Tables 42-4 and 42-5 describe general monitoring recommendations, rationales, and “sex-specific” laboratory values that may require individualized interpretation.

SoRelle JA et al. Impact of hormone therapy on laboratory values in transgender patients. *Clin Chem.* 2019;65:170. [PMID: 30518663]

D. Long-Term Health Outcomes

Well-designed, large, long-term studies of health outcomes in transgender people are lacking. The largest existing study of mortality is a Dutch retrospective cohort of 966 transfeminine persons and 365 transmasculine persons who were treated with cross-sex hormones, which did not control for a number of risk factors. All-cause as well as cardiovascular, cerebrovascular, and other disease-specific

Table 42–3. Masculinizing hormone therapy.

Androgen	Dosage			Comment
	Initial, Low ¹	Initial, Typical	Maximum, Typical ²	
Testosterone cypionate ³	20 mg/week intramuscularly or subcutaneously	50 mg/week intramuscularly or subcutaneously	100 mg/week intramuscularly or subcutaneously	Double the dose for biweekly administration
Testosterone enanthate ³	20 mg/week intramuscularly or subcutaneously	50 mg/week intramuscularly or subcutaneously	100 mg/week intramuscularly or subcutaneously	
Testosterone topical gel 1%	12.5–25 mg every morning	50 mg every morning	100 mg every morning	May come in pump or packet form.
Testosterone topical gel 1.62% ⁴	20.25 mg every morning	40.5–60.75 mg every morning	103.25 mg every morning	
Testosterone patch	1–2 mg every night	4 mg every night	8 mg every night	Patches come in 2-mg and 4-mg size. For lower doses, may cut patch.
Testosterone cream ⁵	10 mg	50 mg	100 mg	
Testosterone axillary gel 2%	30 mg every morning	60 mg every morning	90–120 mg every morning	Comes in pump only; one pump = 30 mg.
Testosterone undecanoate ⁶	N/A	750 mg intramuscularly, repeat in 4 weeks, then every 10 weeks ongoing	N/A	Requires participation in manufacturer monitored program. ⁶

¹Initial, low-dose regimen is recommended for genderqueer and non-binary persons.

²Maximum dosing does not mean maximal effect. Furthermore, these dosage ranges do not necessarily represent a target or ideal dose. Dose increases or decreases should be based on patient response and monitored hormone levels.

³Available as standard US Pharmacopia (USP) as well as compounded products.

⁴Doses of less than 20.25 mg with 1.62% gel or less than 30 mg with 2% axillary gel may be difficult, since measuring one-half of a pump or packet can present a challenge. Patients requiring doses lower than 20.25 mg and whose insurance does not cover 1% gel may require prior authorization or an appeal.

⁵Testosterone creams are prepared by individual compounding pharmacies. Specific absorption and activity varies and consultation with the individual compounding pharmacist is recommended.

⁶Testosterone undecanoate has been associated with rare cases of pulmonary oil microembolism and anaphylaxis; in the United States, the drug is available only through the AVEED Risk Evaluation and Mitigation Strategy (REMS) Program (<https://www.aveedrems.com/AveedUI/rems/preHome.action>). All injections must be administered in an office or hospital setting by a trained and registered health care provider and monitored for 30 minutes afterward for adverse reactions.

Table 42–4. Laboratory monitoring for feminizing hormone therapy.

	Comments	Baseline	3 Months ¹	6 Months ¹	12 Months ¹	Yearly	As needed
Blood urea nitrogen/creatinine/potassium	Only if spironolactone is used	X	X	X	X	X	
Lipids		X (if clinically indicated)		X	X		X
Hemoglobin A _{1C}		X		X	X	X	
Estradiol			X	X			X
Total testosterone			X	X	X		X
Sex hormone binding globulin (SHBG) ²			X	X	X		X
Albumin ²			X	X	X		X
Prolactin	Only if symptomatic						X

¹In first year of therapy only.

²Used to calculate bioavailable testosterone (<http://www.issam.ch/freetesto.htm>).

Table 42–5. Laboratory monitoring for masculinizing hormone therapy.

	Comments	Baseline ¹	3 Months ²	6 Months ²	12 Months ²	Yearly	As Needed
Lipids	No evidence	X		X	X	X	X
Hemoglobin A _{1c} or fasting glucose		X		X	X	X	
Estradiol							X
Total testosterone			X	X	X		X
Albumin ³			X	X	X		X
Hemoglobin and hematocrit		X	X	X	X	X	X

¹Based on United States Prevention Services Task Force guidelines.

²In first year of therapy only.

³Used to calculate bioavailable testosterone.

mortality among transmasculine persons did not differ from the general Dutch population of cisgender women. Among transfeminine persons, all-cause mortality was 51% higher than cisgender men in the general Dutch population, with the overwhelming majority of the difference due to HIV, drug overdose, and suicide; a 64% increased risk (95% CI 43–87%) in cardiovascular mortality was seen; however, no significant difference was seen for cerebrovascular mortality. It should be noted that this study did not control for tobacco use. A retrospective cohort study of several thousand transmasculine and transfeminine persons enrolled in a large health plan in the United States found modest increases in cardiovascular, cerebrovascular, and venous thromboembolic events in transfeminine persons compared to a matched control group. Outcomes were not adjusted for dose or route of estrogen administration, however, and the absolute risk difference was low, with numbers needed to harm in the 80 to 120 range for various outcomes. No statistically significant difference was found in any of these outcomes in transmasculine persons compared to controls. Any decisions to provide hormone therapy should include a detailed informed consent discussion and consideration, including recognizing the significant risks of withholding treatment on psychological well being which can have negative impacts on physical health as well as suicidality or substance abuse.

Asschelman H et al. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011;164:635. [PMID: 21266549]

Getahun D et al. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. Ann Intern Med. 2018;169:205. [PMID: 29987313]

Libman H et al. Caring for the transgender patient: grand rounds discussion from Beth Israel Deaconess Medical Center. Ann Intern Med. 2020;172:202. [PMID: 32016334]

► Cancer Risk & Screening

Several retrospective studies have not identified an increased risk of cancer in transgender people compared to birth-sex matched controls. However, because of the numerous barriers to care as well as to identifying transgender people in clinical databases, underscreening and underreporting are likely. In general, an organ-based approach to screening should be taken. There are no modifications to screening recommendations (or recommendations not to screen) for ovarian, uterine, or cervical cancer in transmasculine persons. Breast cancer screening for transmasculine people who have not undergone mastectomy should be performed based on guidelines for cisgender women. The role of screening for breast cancer in transmasculine people who have undergone mastectomy is unknown and depends on the technique used as well as technical limitations on screening small amounts of

Table 42–6. Procedural interventions for gender affirmation.

Surgeries specific to transgender populations

Voice surgery

Feminizing procedures:

Facial feminization procedures

Reduction thyrochondroplasty (tracheal cartilage shave)

Vaginoplasty

Masculinizing procedures:

Phalloplasty, scrotoplasty

Metaoidioplasty (clitoral release/enlargement, may include urethral lengthening)

Masculinizing chest surgery ("top surgery")

Surgeries not specific to transgender populations

Augmentation mammoplasty

Hysterectomy, oophorectomy

Orchiectomy

Vaginectomy

Other interventions

Facial hair removal

Voice modification

Genital tucking and packing

Chest binding

► Surgical Interventions

A wide range of gender-affirming surgeries are available to transgender people. These include surgeries specific to gender affirmation as well as procedures commonly performed in cisgender populations (Table 42–6).

residual breast tissue. In transfeminine people, breast cancer screening using guidelines for cisgender women is recommended, with the modifications starting at age 50 and only after a minimum of 5 years of lifetime estrogen exposure. Screening for prostate cancer in transfeminine people is complicated beyond the current debate over the utility of prostate cancer screening in cisgender men by the effects of feminizing hormones on prostatic hypertrophy and interpretation of tests of prostate-specific antigen.

UCSF Center of Excellence for Transgender Health. Guidelines for the Primary and Gender Affirming Care of Transgender and Gender Nonconforming People. <https://transcare.ucsf.edu/guidelines>

Wierckx K et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013;169:471. [PMID: 23904280]

can result in survival transactional sex and sex work, and an association between unaffirmed gender identity and high-risk sexual behavior. Based on studies of hormonal contraception, gender-affirming hormone therapy is not believed to have negative interactions with antiretroviral medications, although direct studies are lacking. A sub-analysis of transfeminine persons within a larger study of HIV PrEP with a daily fixed-dose combination of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg suggested efficacy when taken as prescribed but demonstrated poor adherence in comparison to control MSM. Such findings support the notion that HIV services and programs targeting transgender populations should be developed and implemented distinctly from those targeting MSM, and that bundling of HIV care with gender-affirming care may improve HIV outcomes.

Deutsch MB et al; iPrEx investigators. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. *Lancet HIV*. 2015;2:e512 [PMID: 26614965]

Poteat T et al. HIV risk and preventive interventions in transgender women sex workers. *Lancet*. 2015;385:274. [PMID: 25059941]
Sevelius JM. Gender affirmation: a framework for conceptualizing risk behavior among transgender women of color. *Sex Roles*. 2013;68:675. [PMID: 23729971]

► HIV

Transfeminine persons in the United States are 34 times more likely to be infected with HIV than the general population. This disparity is driven by a number of factors, including lack of both employment opportunities and legal protections in the workplace and elsewhere, all of which

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YEAR IN REVIEW: KEY CLINICAL UPDATES IN CMDT 2022

Topic	New Advances Affecting Clinical Practice*
WARTS Page 143	<ul style="list-style-type: none"> Sinecatechins (10% or 15%) is FDA approved for the treatment of anogenital warts. Application three times daily for 16 weeks achieves clearance rates from 40% to 81%, with the 15% formulation resulting in higher efficacy. <p>Jung JM et al. <i>Br J Dermatol.</i> [PMID: 31675442]</p>
AGE-RELATED MACULAR DEGENERATION Page 185	<ul style="list-style-type: none"> Brolucizumab, an inhibitor of vascular endothelial growth factor, has been associated with intraocular inflammation and occlusive retinal vasculitis, resulting in irreversible vision loss in some patients. <p>Baumal CR et al. <i>Ophthalmology.</i> [PMID: 32344075]</p>
ADVERSE OCULAR EFFECTS OF SYSTEMIC DRUGS Page 197	<ul style="list-style-type: none"> Pentosan polysulfate (used to treat interstitial cystitis) has been associated with progressive vision loss due to maculopathy. Patients who receive pentosan polysulfate should be monitored with annual eye examinations. <p>Pearce WA et al. <i>Ophthalmology.</i> [PMID: 29801663]</p>
ASTHMA Page 243	<ul style="list-style-type: none"> The pathophysiology of asthma is heterogeneous, but a division into T2-high and T2-low endotypes (marked by high and low levels of classic Th2 cytokines, including IL-4, IL-5, and IL-13, respectively) has been shown to be important regarding the selection of therapies. <p>Schoettler N et al. <i>Chest.</i> [PMID: 31678077]</p>
ASTHMA Pages 243	<ul style="list-style-type: none"> Allergic asthma falls into the T2-high endotype, as do late-onset T2-high asthma and aspirin/NSAID-associated respiratory disease. T2-low asthma phenotypes include nonallergic asthma, which tends to occur in adults and be marked by neutrophilic inflammation and variable response to standard therapies. <p>Schoettler N et al. <i>Chest.</i> [PMID: 31678077]</p>
BRONCHIOLITIS Page 266	<ul style="list-style-type: none"> Azithromycin may be used to treat diffuse panbronchiolitis; it may also slow down the progression of bronchiolitis obliterans syndrome in lung transplant recipients. <p>Gan CT et al. <i>BMJ Open Respir Res.</i> [PMID: 31673366]</p>
COMMUNITY-ACQUIRED PNEUMONIA Page 270	<ul style="list-style-type: none"> Procalcitonin is not recommended as a “rule-out” test for bacterial pneumonia; studies have not found a threshold at which bacterial pneumonia can be reliably distinguished from viral pneumonia based on procalcitonin levels. Empiric antibacterial agents are recommended regardless of procalcitonin level at time of presentation. <p>Ebell MH et al. <i>Acad Emerg Med.</i> [PMID: 32100377]</p>
COMMUNITY-ACQUIRED PNEUMONIA Page 272	<ul style="list-style-type: none"> Based on limited data and because of the potential for complications (eg, hyperglycemia), the Infectious Diseases Society of America/American Thoracic Society guidelines recommend against corticosteroids in the treatment community-acquired pneumonia (CAP) of any severity. Corticosteroids are recommended for patients with CAP who may also have severe septic shock, acute exacerbation of asthma or chronic obstructive pulmonary disease, or adrenal insufficiency. <p>Metlay JP et al. <i>Am J Respir Crit Care Med.</i> [PMID: 31573350]</p>
PULMONARY TUBERCULOSIS Page 280	<ul style="list-style-type: none"> In view of the rapidity of rifampin resistance identification, the World Health Organization issued continued guidance in 2020 that rapid molecular testing is the ideal initial test for diagnosis and resistance profiling in persons in whom pulmonary or extrapulmonary tuberculosis is suspected. <p>https://www.who.int/health-topics/tuberculosis/ https://www.who.int/health-topics/tuberculosis/</p>
PULMONARY VENOUS THROMBOEMBOLISM Page 300	<ul style="list-style-type: none"> Direct-acting oral anticoagulants are recommended as first-line anticoagulation for most patients. <p>Konstantinides SV et al. <i>Eur Heart J.</i> [PMID: 31473594]</p>
PULMONARY VENOUS THROMBOEMBOLISM Page 300	<ul style="list-style-type: none"> Discontinuation of anticoagulation may be considered after 3 months for patients <ul style="list-style-type: none"> With major transient/reversible risk factors (such as fracture of lower limb; hip or knee surgery) Who were hospitalized because of heart failure, atrial fibrillation, or myocardial infarction. <p>Kearon C et al. <i>Blood.</i> [PMID: 31917402]</p>

*See chapter for further details and references.

(continued on following page)

Topic	New Advances Affecting Clinical Practice*
PULMONARY VENOUS THROMBOEMBOLISM Page 300	<ul style="list-style-type: none"> Guidelines support systemic thrombolysis for high-risk or massive pulmonary embolism (PE) (hemodynamically unstable) with low risk of bleeding. Intermediate-risk or submassive PE patients have a significant decrease in incidence of hemodynamic collapse but do not have a mortality benefit with thrombolytic therapy. They do, however, have an increase in major hemorrhagic complications, including intracranial hemorrhage. <p>Konstantinides SV et al. <i>Eur Heart J.</i> [PMID: 31473594]</p>
PULMONARY HYPERTENSION Page 302	<ul style="list-style-type: none"> A 2020 expert consensus survey has provided recommendations for treatment using oral prostacyclin analogs. <p>McLaughlin VV et al. <i>Chest.</i> [PMID: 31738929]</p>
RADIATION PNEUMONITIS Page 309	<ul style="list-style-type: none"> Months to years after radiation therapy, an occasional patient will experience "radiation recall," an inflammatory reaction in the radiated region after treatment with immune checkpoint inhibitors. <p>Teng F et al. <i>BMC Med.</i> [PMID: 32943072]</p>
PNEUMOTHORAX Page 315	<ul style="list-style-type: none"> A 2020 study demonstrated that a moderate to large pneumothorax in a stable patient (no oxygen requirement, no limitation to ambulation, and no increase in size of pneumothorax over 4 hours of monitoring) who is reliable can be managed without intervention. <p>Brown SGA et al; PSP Investigators. <i>N Engl J Med.</i> [PMID: 31995686]</p>
COARCTATION OF THE AORTA Page 325	<ul style="list-style-type: none"> The 2020 European Society of Cardiology guidelines suggest that stenting is appropriate if the patient is normotensive but has a peak gradient of > 20 mm Hg (class IIa) or if angiography shows stenosis is > 50% (class IIb). <p>Baumgartner H et al. <i>Eur Heart J.</i> [PMID: 32860028]</p>
ATRIAL SEPTAL DEFECT & PATENT FORAMEN OVALE Page 328	<ul style="list-style-type: none"> The 2020 European Society of Cardiology (ESC) guidelines add the pulmonary vascular resistance (PVR) to their criteria and consider it a class IIa indication if the PVR is between 3 Wood units and 5 Wood units; the guidelines preclude the use of closure if the PVR is ≥ 5 Wood units. Rather than using acute testing, ESC guidelines favor bringing the patient back to the catheterization laboratory for retesting while on pulmonary vasodilators to see if the PVR can be reduced to < 5 Wood units. The ESC guidelines also suggest considering fenestrated closure in the face of pulmonary hypertension. The use of bosentan or sildenafil is recommended if the PVR is > 5 Wood units and there is a right to left shunt. <p>Baumgartner H et al. <i>Eur Heart J.</i> [PMID: 32860028]</p>
ATRIAL SEPTAL DEFECT & PATENT FORAMEN OVALE Page 328	<ul style="list-style-type: none"> A 2020 update from the American Academy of Neurology guideline subcommittee reaffirms no change in the policy that states patients < 55 years with cryptogenic stroke/transient ischemic attack (TIA) and no other identifiable cause except for the presence of a patent foramen ovale (PFO) should still be considered for PFO closure. The presence of a "floppy atrial septum - atrial septal aneurysm" has been associated with a higher risk of recurrent stroke/TIA in patients with cryptogenic stroke/TIA. <p>Messé SR et al. <i>Neurology.</i> [PMID: 32350058]</p>
MITRAL REGURGITATION Page 338	<ul style="list-style-type: none"> Transcatheter edge-to-edge repair is an option in symptomatic patients at higher surgical risk regardless of whether the mitral regurgitation is primary or secondary. Patients with functional chronic mitral regurgitation may improve with biventricular pacing and guideline-directed management and therapy. <p>Otto CM et al. <i>J Am Coll Cardiol.</i> [PMID: 33342587]</p>
AORTIC STENOSIS Page 345	<ul style="list-style-type: none"> Surgery is recommended for patients < 65 years or with a life expectancy of > 20 years. Transcatheter aortic valve replacement (AVR) is recommended for all patients > 80 years. Either surgical AVR or transcatheter AVR can be considered for all patients 65–80 years old. <p>Otto CM et al. <i>J Am Coll Cardiol.</i> [PMID: 33342587]</p>
ATRIAL FIBRILLATION Page 395	<ul style="list-style-type: none"> In patients with recent-onset atrial fibrillation (< 1 year), the EAST-AFNET 4 trial found that rhythm control with antiarrhythmic medication or catheter ablation is associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization for heart failure. <p>Kirchhof P et al; EAST-AFNET 4 Trial Investigators. <i>N Engl J Med.</i> [PMID: 32865375]</p>

*See chapter for further details and references.

Topic	New Advances Affecting Clinical Practice*
HEART FAILURE Page 410	<ul style="list-style-type: none"> Two large clinical trials of patients with type 2 diabetes have shown that inhibitors of sodium-glucose linked transporter 2 (SGLT2) substantially reduce the risk of cardiovascular death and hospitalization for heart failure for patients with reduced ejection fraction (EF), with or without diabetes. Dapagliflozin also reduced all-cause mortality and has been approved for treating heart failure with reduced EF. Empagliflozin is under FDA review. While SGLT2 inhibitors also reduced kidney disease progression, patients with severe kidney impairment were not included in these trials. <p>Packer M et al. <i>N Engl J Med.</i> [PMID: 32865377]</p>
HEART FAILURE Page 410	<ul style="list-style-type: none"> In 2021, the FDA approved vericiguat to reduce the risk of cardiovascular death and heart failure hospitalization following hospitalization for heart failure in patients with chronic heart failure and ejection fraction < 45%. The VICTORIA trial showed a modest but significant reduction in cardiovascular death and heart failure hospitalization with vericiguat, concomitant with other effective therapies, in this high-risk population. <p>Armstrong PW et al; VICTORIA Study Group. <i>N Engl J Med.</i> [PMID: 32222134]</p>
INFECTIOUS MYOCARDITIS Page 414	<ul style="list-style-type: none"> COVID-19 myocarditis has been reported between 3% and 58% of infected people based on underlying myocardial risk and imaging. <p>Puntmann VO et al. <i>JAMA Cardiol.</i> [PMID: 32730619]</p>
INFECTIOUS MYOCARDITIS Page 416	<ul style="list-style-type: none"> For COVID-19-related myocarditis, treatment is generally supportive. A 2020 review noted that of the attempted therapies, such as remdesivir, glucocorticoids, IL-6 inhibitors (tocilizumab), intravenous immunoglobulin, and colchicine, only corticosteroids appeared to have any favorable effect on outcomes. <p>Siripanthong B et al. <i>Heart Rhythm.</i> [PMID: 32387246]</p>
HYPERTROPHIC CARDIOMYOPATHY Page 423	<ul style="list-style-type: none"> The following classes detail the 2020 American Heart Association/American College of Cardiology guidelines for a preventive implantable cardioverter defibrillator (ICD): <ul style="list-style-type: none"> Class I: Patients with documented cardiac arrest or sustained ventricular tachycardia. Class IIa: (1) sudden death in ≥ 1 first-degree or close relative ≤ 50 years of age, (2) any left ventricular (LV) wall ≥ 30 mm, (3) any recent syncope likely to have been arrhythmogenic, (4) LV apical aneurysm, or (5) LV systolic dysfunction (ejection fraction < 50%). Class IIb: Presence of a significant (> 15%) late gadolinium enhancement on cardiac MRI. In those who receive an ICD, antitachycardia pacing should be programmed to minimize shocks. The use of an ICD is contraindicated, though, if the purpose is simply to allow for the patient to play competitive sports. <p>Ommen SR. <i>Circulation.</i> [PMID: 33215938]</p>
RESTRICTIVE CARDIOMYOPATHY Page 424	<ul style="list-style-type: none"> Tafamidis helps prevent the misfolding of the TTR tetramer and is approved for treatment. Patisiran is also available, and it inhibits both variant and wild type TTR production. For the variant TTR polyneuropathy, subcutaneous inotersen is available (it binds to TTR mRNA preventing transcription). <p>Marques N et al. <i>J Am Heart Assoc.</i> [PMID: 32969287]</p>
SYSTEMIC HYPERTENSION Page 466	<ul style="list-style-type: none"> The SPYRAL HTN-OFF MED study used a controlled ablation strategy to perform renal sympathetic denervation; clinically meaningful blood pressure reductions occurred in the intervention group compared to the control group. Although not yet accepted in general clinical practice, renal sympathetic nerve ablation may emerge as an alternative or adjunctive modality in the treatment of hypertension and may become useful in managing resistant hypertension and drug intolerance. <p>Böhm M et al. <i>Lancet.</i> [PMID: 32234534]</p>
SYSTEMIC HYPERTENSION Page 466	<ul style="list-style-type: none"> The HYgia trial compared the effect of nighttime dosing of at least one antihypertensive medication with morning dosing of all antihypertensive medications in 19,000 participants with median follow up 6.3 years and demonstrated improved ambulatory blood pressure and a significant decline in major cardiovascular events in the nighttime dosing group. Participants in the HYgia were monitored via ambulatory blood pressure measurement, and the incidence of nocturnal hypotension was very low. However, profound nocturnal hypotension might not be detected in the absence of ambulatory blood pressure monitoring, and ischemic optic neuropathy or other low perfusion complications would be a concern. <p>Hermida RC et al; Hygia Project Investigators. <i>Eur Heart J.</i> [PMID: 31641769]</p>
SYSTEMIC HYPERTENSION Page 469	<ul style="list-style-type: none"> Canagliflozin generally lowers blood pressure by 3–4 mm Hg in addition to providing better glycemic control through inhibition of the sodium-glucose linked transporter 2 (SGLT2) glucose transporter in patients with diabetes. This drug was associated with improved renal outcomes and reduced cardiovascular risk in the CREDENCE trial of patients with diabetic nephropathy and can be considered when additional blood pressure control is needed in patients with type 2 diabetes. <p>Perkovic V et al; CREDENCE Trial Investigators. <i>N Engl J Med.</i> [PMID: 30990260]</p>

*See chapter for further details and references.

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Topic	New Advances Affecting Clinical Practice *
OCCLUSIVE DISEASE: AORTA & ILLIAC ARTERIES Page 476	<ul style="list-style-type: none"> Low-dose rivaroxaban (2.5 mg orally twice daily) with aspirin 100 mg orally daily reduces both major cardiovascular and limb-related adverse events in symptomatic patients. <i>Bonaca MP et al. N Engl J Med. [PMID: 32222135]</i>
OCCLUSIVE DISEASE: FEMORAL & POPLITEAL ARTERIES Page 477	<ul style="list-style-type: none"> When a meta-analysis of clinical trial data showed increased mortality at 3–5 years after treatment with paclitaxel-coated devices, the FDA performed an independent review and recommends judicious use of the devices. Ongoing trials, such as SWEDEPAD, are expected to provide additional data on the risks and benefits of paclitaxel devices. <i>Nordanstig J et al. N Engl J Med. [PMID: 33296560]</i>
THE THALASSEMIAS Page 508	<ul style="list-style-type: none"> Luspatercept has been FDA approved for transfusion-dependent beta-thalassemia. It is a TGF-beta ligand trap that promotes erythroid maturation and reduces transfusion needs. <i>Cappellini MD et al. N Engl J Med. [PMID: 32212518]</i>
SICKLE CELL ANEMIA & RELATED SYNDROMES Page 515	<ul style="list-style-type: none"> Voxelotor inhibits the polymerization of deoxygenated sickle red blood cells and increases the hemoglobin in SS patients age 12 years or older. <i>Vichinsky E et al. N Engl J Med. [PMID: 31199090]</i>
POLYCYTHEMIA VERA Page 523	<ul style="list-style-type: none"> Ropeginterferon alfa-2b was approved by the European Medicines Agency as first-line therapy for patients with polycythemia vera without symptomatic splenomegaly. <i>Gisslinger H et al; PROUD-PV Study Group. Lancet Haematol. [PMID: 32014125]</i>
ESSENTIAL THROMBOCYTHEMIA Page 524	<ul style="list-style-type: none"> A study found that low-dose aspirin (81 mg/day orally) was not as effective as an every 12-hour regimen in reducing the risk of thrombotic complications in low-risk patients. <i>Rocca B et al. Blood. [PMID: 32266380]</i>
MYELODYSPLASTIC SYNDROMES Page 529	<ul style="list-style-type: none"> A novel agent, luspatercept, has been developed to target signaling via the SMAD2–SMAD3 pathway which is constitutively increased in the bone marrow cells of patients with myelodysplastic syndrome (MDS) and ineffective erythropoiesis. In a randomized study, luspatercept induced transfusion independence in 38% of lower-risk MDS patients who did not respond to growth factor therapy compared to 13% in the placebo arm. <i>Fenaux P et al. N Engl J Med. [PMID: 31914241]</i>
ACUTE MYELOID LEUKEMIA Page 531	<ul style="list-style-type: none"> Patients with a FLT3 mutation benefit from the addition of the FLT3 kinase inhibitor midostaurin to their regimen. Patients with secondary acute myeloid leukemia (AML) (evolved from prior myelodysplastic or myeloproliferative disorders) or treatment-associated AML should receive the medication Vyxeos (a liposomal formulation of daunorubicin and cytarabine). <i>DiNardo CD et al. Blood. [PMID: 31765470]</i>
ACUTE MYELOID LEUKEMIA Page 531	<ul style="list-style-type: none"> Patients > 75 years of age who are not treated with initial curative intent can derive benefit from newer targeted agents, including the bcl2 inhibitor venetoclax added to a hypomethylating agent or low-dose cytarabine, enasidenib (targeting IDH2 mutations), ivosidenib (targeting IDH1 mutations), or glasdegib. <i>Sekeres MA et al. Blood Adv. [PMID: 32761235]</i>
HODGKIN LYMPHOMA Page 537	<ul style="list-style-type: none"> ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy remains the standard first-line regimen. The substitution of the antibody-drug conjugate brentuximab vedotin for bleomycin (AAVD) has demonstrated superior progression-free survival to ABV but no change in overall survival. <i>Huntington SF. Hematology Am Soc Hematol Educ Program. [PMID: 31808838]</i>
PLASMA CELL MYELOMA Page 540	<ul style="list-style-type: none"> Belantamab mafodotin (an anti-BCMA antibody conjugated to a cytotoxic agent) is as effective as salvage therapy after relapse. <i>Lonial S et al. Lancet Oncol. [PMID: 31859245]</i>
AMYLOIDOSIS Page 543	<ul style="list-style-type: none"> Therapy for AA amyloid is treatment of the underlying cause of inflammation. Treatment of familial TTR is liver transplantation and of acquired TTR is tafamidis or inotersen. <i>Gertz MA et al. JAMA. [PMID: 32633805]</i>
THROMBOTIC MICROANGIOPATHY Page 554	<ul style="list-style-type: none"> The role of caplacizumab in the treatment of thrombotic thrombocytopenic purpura remains controversial given its high cost and limited benefit, despite its inclusion in 2020 guidelines. <i>Zheng XL et al. J Thromb Haemost. [PMID: 32914526]</i>

*See chapter for further details and references.

Topic	New Advances Affecting Clinical Practice*
THROMBOTIC MICROANGIOPATHY Page 554	<ul style="list-style-type: none"> Careful monitoring of the ADAMTS-13 activity and inhibitor status and use of rituximab can prevent dangerous relapses. <p><i>Zheng XL et al. J Thromb Haemost. [PMID: 32914526]</i></p>
NAUSEA & VOMITING Page 584	<ul style="list-style-type: none"> A 2020 American Gastroenterological Association meta-analysis reported a pooled prevalence of nausea or vomiting (usually mild) in 7.8% of patients with acute COVID-19. Up to 16% of patients with acute COVID-19 may present with gastrointestinal symptoms (anorexia, nausea, diarrhea) in the absence of respiratory symptoms. <p><i>Sultan S et al. Gastroenterology. [PMID: 32407808]</i></p>
ACUTE UPPER GASTROINTESTINAL BLEEDING Page 601	<ul style="list-style-type: none"> Compared with surgical intervention for recurrent or refractory bleeding, embolization achieves equivalent clinical success rates with lower mortality. <p><i>Mullady DK et al. Gastroenterology. [PMID: 32574620]</i></p>
OCCULT GASTROINTESTINAL BLEEDING Page 604	<ul style="list-style-type: none"> A 2020 American Gastroenterological Association guidelines recommends an initial trial of empiric iron therapy for patients with iron deficiency anemia who have no significant findings on upper endoscopy or colonoscopy and who are without symptoms of small intestinal disease. A sustained rise in ferritin and hemoglobin with 1–2 months of iron therapy may obviate the need for further studies. Further investigation of the small intestine is recommended in patients who have anemia that responds poorly to empiric iron supplementation, who have signs of ongoing bleeding (fecal occult blood) or who have worrisome symptoms (abdominal pain, weight loss). Capsule endoscopy is recommended as the initial study in most patients to look for vascular ectasias and to exclude a small intestinal neoplasia or inflammatory bowel disease. <p><i>Ko CW et al. Gastroenterology. [PMID: 32810434]</i></p>
ACHALASIA Page 622	<ul style="list-style-type: none"> Pneumatic dilation, Heller cardiomyotomy, and peroral endoscopic myotomy (POEM) provide comparable short- and long-term symptomatic improvement in achalasia types I or II. For type III (spastic) achalasia, POEM with a long distal myotomy may be preferred to Heller cardiomyotomy where expertise is available. <p><i>Carlson DA et al. Am J Gastroenterol. [PMID: 32558688]</i> <i>Khashab M et al. Gastrointest Endosc. [PMID: 31839408]</i> <i>Vaezi MF et al. Am J Gastroenterol. [PMID: 32773454]</i></p>
ULCERATIVE COLITIS Page 663	<ul style="list-style-type: none"> For patients who require more than one course of corticosteroid therapy every 1–2 years for symptomatic relapse, treatment should be 'stepped up' to include a thiopurine (azathioprine or mercaptopurine) or a biologic agent. <p><i>Singh S et al. Clin Gastroenterol Hepatol. [PMID: 31945470]</i></p>
ULCERATIVE COLITIS Page 663	<ul style="list-style-type: none"> A 2020 American Gastroenterological Association guideline recommends either infliximab or vedolizumab as first-line therapies for moderate to severe colitis based on their efficacy and safety profiles. These two agents had the highest rankings of all biologic agents for induction of clinical remission in a 2020 network meta-analysis. Although infliximab may be the more effective agent (especially for severe disease), vedolizumab may be the preferred first-line therapy in patients who are elderly or have increased medical comorbidities due to its significantly lower incidence of infectious complications. <p><i>Feuerstein JD et al. Gastroenterology. [PMID: 30576644]</i></p>
NONFAMILIAL ADENOMATOUS & SERRATED POLYPS Page 669	<ul style="list-style-type: none"> The US Multi-Society Task Force Guideline provides the following recommendations for repeat colonoscopy that depend on the findings at baseline colonoscopy: 10 years: normal colonoscopy or fewer than 20 hyperplastic polyps < 10 mm in the distal colon or rectum <ul style="list-style-type: none"> 7–10 years: 1–2 adenomas < 10 mm 5–10 years: 1–2 sessile serrated polyps < 10 mm 3–5 years: 3–4 adenomas or sessile serrated polyps < 10 mm 3 years: 5–10 adenomas or sessile serrated polyps < 10 mm; or 1 or more adenomas or sessile serrated polyp ≥ 10 mm or an adenoma containing villous features or high-grade dysplasia or a sessile serrated polyp with dysplasia. <p><i>Gupta S et al. Gastroenterology. [PMID: 32039982]</i></p>

*See chapter for further details and references.

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Topic	New Advances Affecting Clinical Practice*
HEPATIC VENOUS OUTFLOW OBSTRUCTION (BUDD-CHIARI SYNDROME) Page 718	<ul style="list-style-type: none"> When transjugular intrahepatic portosystemic shunt is technically not feasible because of complete hepatic vein obstruction, ultrasound-guided direct intrahepatic portosystemic shunt is an alternative approach. <p><i>Simonetto DA et al. Am J Gastroenterol. [PMID: 31895720]</i></p>
THE LIVER IN HEART FAILURE Page 719	<ul style="list-style-type: none"> Rare cases of ischemic hepatitis, also called ischemic hepatopathy, hypoxic hepatitis, shock liver, or acute cardiogenic liver injury, have occurred in patients with COVID-19. <p><i>Kudaravalli P et al. Eur J Gastroenterol Hepatol. [PMID: 32568805]</i></p>
NONCIRRHOTIC PORTAL HYPERTENSION Page 720	<ul style="list-style-type: none"> Contrast-enhanced computed tomography or magnetic resonance angiography of the portal system can assess extension of thrombus into the mesenteric veins and exclude tumor thrombus in patients with cirrhosis. <p><i>Valla DC. Liver Int. [PMID: 32077611]</i></p>
NONCIRRHOTIC PORTAL HYPERTENSION Page 720	<ul style="list-style-type: none"> The decision to give an anticoagulant to a patient with cirrhosis and portal vein thrombosis depends on the presence of ascites, the patient's fall risk, and the patient's candidacy for liver transplantation. Moreover, partial portal vein thrombosis may resolve in 30–50% of cases. Data on the use of direct-acting oral anticoagulants in patients with cirrhosis and portal vein thrombosis are lacking. <p><i>Valla DC. Liver Int. [PMID: 32077611]</i></p>
CARCINOMA OF THE FEMALE BREAST Page 762	<ul style="list-style-type: none"> In 2020, the FDA approved neratinib (in combination with capecitabine) and margetuximab, a monoclonal antibody similar to trastuzumab that is designed to improve the antibody dependent cellular cytotoxicity mechanism of action when used with chemotherapy. <p><i>Saura C et al. J Clin Oncol. [PMID: 32678716]</i></p>
CARCINOMA OF THE FEMALE BREAST Page 763	<ul style="list-style-type: none"> In 2020, pembrolizumab, a second immune checkpoint inhibitor, was FDA approved for use in patients with PD-L1 positive disease in combination with chemotherapy (taxane or gemcitabine/carboplatin) based on results from the KEYNOTE 355 trial showing an improved median progression-free survival with the addition of this antibody to standard chemotherapy. <p><i>Cortes J et al. Lancet. 2020;396:1817. [PMID: 33278935]</i></p>
CARCINOMA OF THE FEMALE BREAST Page 763	<ul style="list-style-type: none"> Sacituzumab govitecan (TRODELVY) is the first antibody drug conjugate approved for triple negative breast cancer. The phase 3 confirmatory trial, ASCENT, demonstrated that sacituzumab govitecan is associated with a statistically significant improvement in progression-free and overall survival when compared to single-agent chemotherapy in patients with triple negative breast cancer who had received at least two prior lines of standard chemotherapy for metastatic disease. <p><i>Bardia A, Hurvitz SA et al. N Engl J Med. 2021;384:1529. [PMID: 33882206]</i></p>
CONTRACEPTIVE FOAM, CREAM, FILM, SPONGE, JELLY, & SUPPOSITORY Page 784	<ul style="list-style-type: none"> A different on-demand vaginal contraceptive, a vaginal pH regulator gel containing lactic acid-citric acid-potassium bitartrate (Phexxi), was FDA approved for use in the United States in 2020. In a clinical study of the efficacy of Phexxi, the 7-cycle cumulative pregnancy risk was 7% when used as directed and 14% with typical use. <p><i>Phexxi—a nonhormonal contraceptive gel. Med Lett Drugs Ther. [PMID: 32970042]</i></p>
PREECLAMPSIA-ECLAMPSIA Page 807	<ul style="list-style-type: none"> Gestational hypertension is defined as blood pressure of $\geq 140/90$ mm Hg systolic or > 90 mm Hg diastolic after 20 weeks of gestation. Gestational hypertension may be present in the absence of proteinuria. <p><i>American College of Obstetricians and Gynecologists. Obstet Gynecol. [PMID: 32443079]</i></p>
PREECLAMPSIA-ECLAMPSIA Page 808	<ul style="list-style-type: none"> Like preeclampsia-eclampsia without severe features, gestational hypertension is managed by delivery. <p><i>American College of Obstetricians and Gynecologists. Obstet Gynecol. [PMID: 32443079]</i></p>
MATERNAL HEPATITIS B & C CARRIER STATE Page 821	<ul style="list-style-type: none"> There is one open-label, phase 1 study of pregnant women with hepatitis C treated with ledipasvir-sofosbuvir for 12 weeks starting in the second trimester. Although the study was small (nine participants), ledipasvir-sofosbuvir was safe and effective at the standard dose. <p><i>Chappell CA et al. Lancet Microbe. [PMID: 32939459]</i></p>

*See chapter for further details and references.

Topic	New Advances Affecting Clinical Practice*
INTRAHEPATIC CHOLESTASIS OF PREGNANCY Page 823	<ul style="list-style-type: none"> The use of ursodeoxycholic acid is not recommended for the treatment of intrahepatic cholestasis of pregnancy; a randomized controlled trial did not find that ursodeoxycholic acid reduced symptoms and morbidity for intrahepatic cholestasis of pregnancy. <i>Chappell LC et al; PITCHES study group. Lancet. [PMID: 31378395]</i>
DEGENERATIVE JOINT DISEASE (OSTEOARTHRITIS) Page 827	<ul style="list-style-type: none"> A randomized, controlled trial of 156 individuals with knee osteoarthritis found that physical therapy was more effective at reducing pain and disability at 1 year than intra-articular glucocorticoid injections. <i>Deyle GD et al. N Engl J Med. [PMID: 32268027]</i>
CRYSTAL DEPOSITION ARTHRITIS Page 829	<ul style="list-style-type: none"> In a 2020 randomized, controlled trial in patients with chronic kidney disease and a high risk of its progression, urate-lowering treatment with allopurinol did not slow the decline in estimated glomerular filtration rate when compared to placebo. <i>Badve SV et al; CKD-FIX Study Investigators. N Engl J Med. [PMID: 32579811]</i>
CRYSTAL DEPOSITION ARTHRITIS Page 831	<ul style="list-style-type: none"> In patients with concomitant coronary artery disease, long-term colchicine use can reduce major cardiovascular events. <i>Nidorf SM et al; LoDoCo2 Trial Investigators. N Engl J Med. [PMID: 32865380]</i>
CRYSTAL DEPOSITION ARTHRITIS Page 832	<ul style="list-style-type: none"> Despite initial concern that febuxostat was associated with more cardiovascular events than allopurinol, a large, randomized, controlled trial in 2020 showed that the two medications have similar cardiovascular safety. <i>Mackenzie IS et al; FAST Study Group. Lancet. [PMID: 33181081]</i>
IMMUNE-MEDIATED INFLAMMATORY MYOPATHIES Page 849	<ul style="list-style-type: none"> Idiopathic inflammatory myopathies <ul style="list-style-type: none"> Include polymyositis, dermatomyositis, myositis resulting from a rheumatic disease or overlap syndrome, inclusion body myositis (IBM), and immune-mediated necrotizing myopathy. These disorders are characterized by progressive muscle weakness, and all but IBM demonstrate an inflammatory infiltrate in muscle tissue. Inclusion body myositis is associated with antibodies to cytoplasmic 5'-nucleotidase 1A (cN1A) Immune-mediated necrotizing myopathy is associated with anti-SRP antibodies and anti-HMGCR antibodies <p><i>Allenbach Y et al. Nat Rev Rheumatol. [PMID: 33093664]</i></p>
GRANULOMATOSIS WITH POLYANGIITIS Page 859	<ul style="list-style-type: none"> Plasma exchange does not reduce the incidence of end-stage kidney disease or death in severe ANCA-associated vasculitis. <i>Walsh M et al. N Engl J Med. [PMID: 32053298]</i>
LEVAMISOLE-ASSOCIATED PURPURA Page 861	<ul style="list-style-type: none"> There may be long-term sequelae of levamisole exposure, such as deforming cutaneous lesions, arthralgias, and arthritis. <i>Emil NS et al. J Clin Rheumatol. [PMID: 30273264]</i>
RELAPSING POLYCHONDRITIS Page 862	<ul style="list-style-type: none"> Large vessel vasculitis is a frequently overlooked but potentially catastrophic complication. <i>Tomelleri A et al. J Rheumatol. [PMID: 31839593]</i>
ACUTE PYOGENIC OSTEOMYELITIS Page 872	<ul style="list-style-type: none"> Combined with surgical debridement, a 3-week course of antibiotics (compared to 6 weeks) may be sufficient. <i>Gariani K et al. Clin Infect Dis. [PMID: 33242083]</i>

*See chapter for further details and references.

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Topic	New Advances Affecting Clinical Practice*
COVID-19 & THE KIDNEY Page 922	<ul style="list-style-type: none"> Nearly half of patients hospitalized with COVID-19 present with or develop acute kidney injury (AKI), which is associated with poorer prognosis. The most common cause of AKI in patients with COVID-19 is acute tubular necrosis related to a high inflammatory state (termed “cytokine storm”). Treatment of COVID-19-related AKI is largely supportive. <p><i>Chan L et al. Mount Sinai COVID Informatics Center (MSCIC). J Am Soc Nephrol. [PMID: 32883700]</i> <i>Ronco C et al. Lancet Respir Med. [PMID: 32416769]</i></p>
COVID-19 & THE KIDNEY Page 922	<ul style="list-style-type: none"> Urinalysis may reveal hematuria, reflecting endothelial injury and fibrin thrombi that are commonly observed on biopsy. <p><i>Shetty AA et al. J Am Soc Nephrol. [PMID: 33214201]</i></p>
COVID-19 & THE KIDNEY Page 922	<ul style="list-style-type: none"> COVID-19-associated collapsing glomerulopathy is a type of focal segmental glomerulosclerosis. The role of corticosteroids in COVID-19-associated collapsing glomerulopathy is under investigation. <p><i>Nasr SH et al. Kidney Int Rep. [PMID: 32368701]</i> <i>Ronco C et al. Lancet Respir Med. [PMID: 32416769]</i></p>
IGA NEPHROPATHY Page 936	<ul style="list-style-type: none"> Prior trials suggested that corticosteroids reduced proteinuria when administered to patients with glomerular filtration rate (GFR) > 50 mL/min/1.73 m² and persistent proteinuria > 1 g. However, more recent data failed to demonstrate slowing of GFR loss with corticosteroid therapy compared with use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker alone; enthusiasm for glucocorticoid therapy therefore has waned. <p><i>Rauen T et al. Kidney Int. [PMID: 32450154]</i></p>
PAUCI-IMMUNE GLOMERULONEPHRITIS (ANCA-ASSOCIATED) Page 937	<ul style="list-style-type: none"> Trials using the complement inhibitor avacopan in place of glucocorticoids in cyclophosphamide- or rituximab-based regimens are ongoing and appear promising. <p><i>Serling-Boyd N et al. Curr Opin Rheumatol. [PMID: 33164993]</i></p>
HEMATURIA Page 952	<ul style="list-style-type: none"> Evaluation of the microscopic hematuria is guided by the risk stratification for a urothelial malignancy. The American Urological Association released guidelines for microscopic hematuria workup; patients are categorized as low-, intermediate-, or high-risk for a urothelial malignancy. <p><i>Barocas DA et al. J Urol. [PMID: 32698717]</i></p>
POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME Page 993	<ul style="list-style-type: none"> Management may involve volume repletion, a high salt diet and copious fluids, postural and psychophysiological training, and a graduated exercise program. Medication treatment may include a beta-blocking agent (eg, propranolol), phenobarbital, or clonidine for patients with hyperadrenergic postural orthostatic tachycardia syndrome; and midodrine or fludrocortisone if the blood pressure is low. <p><i>Gibbons CH et al. Heart Rhythm. [PMID: 33482385]</i></p>
DEGENERATIVE MOTOR NEURON DISEASES Page 1037	<ul style="list-style-type: none"> Risdiplam (5 mg orally daily for patients ≥ 2 years of age weighing > 20 kg) is approved for use in infants and adults. <p><i>Norris SP et al. Curr Opin Neurol. [PMID: 32868602]</i></p>
ANTERIOR HYPOPITUITARISM Page 1111	<ul style="list-style-type: none"> Opioid use disorder has become a common cause of functional hypopituitarism. About 63% of long-term opioid (including methadone) users develop partial hypogonadotropic hypogonadism. Opioid use also causes secondary adrenal insufficiency in about 15% of patients but is less likely to cause growth hormone or thyroid deficiency. <p><i>de Vries F et al. J Clin Endocrinol Metab. [PMID: 31511863]</i></p>
THYROID CANCER Page 1148	<ul style="list-style-type: none"> In patients with <i>BRAFV600E</i> mutant anaplastic thyroid cancer, combined BRAF and MEK inhibition with dabrafenib and trametinib has induced durable responses. <p><i>Tiedje V et al. Nat Rev Endocrinol. [PMID: 31819229]</i></p>
OSTEOPOROSIS Page 1163	<ul style="list-style-type: none"> Doses of vitamin D₃ > 4000 international units daily in adults are generally not advised (except in patients with intestinal malabsorption), since gastrointestinal side effects or hypercalcemia may occur. Vitamin D should not be taken with topical calcipotriene to avoid hypercalcemia. <p><i>Camacho PM et al. Endocr Pract. [PMID: 32427503]</i></p>

*See chapter for further details and references.

Topic	New Advances Affecting Clinical Practice*
OSTEOPOROSIS Page 1165	<ul style="list-style-type: none"> The effects of denosumab on bone wane quickly after 6 months and patients can experience a dramatic increased risk of multiple vertebral fractures within 1–2 years following discontinuation of denosumab. Therefore, denosumab must be given on-schedule without drug holidays. Denosumab should not be discontinued without substituting another anti-resorptive agent (bisphosphonate, estradiol, or selective estrogen receptor modulator [SERM]) or other therapy. <p><i>Deal CL. Cleve Clin J Med. [PMID: 32487553] Diker-Cohen T et al. J Clin Endocrinol Metab. [PMID: 31899506]</i></p>
RICKETS & OSTEOMALACIA Page 1168	<ul style="list-style-type: none"> Patients with high fibroblast growth factor 23 (FGF-23) levels can have genetic testing for X-linked hypophosphatemic rickets (<i>PHEX</i>), autosomal dominant hypophosphatemic rickets (<i>FGF23</i>), and autosomal recessive hypophosphatemic rickets (<i>DMP1</i>). In hypophosphatemic patients without such mutations, searching for a tumor causing tumor-induced osteomalacia is reasonable, particularly in patients with bone pain or fractures. Such tumors are typically small and may be located anywhere, so they are best localized using a whole-body DOTATATE-PET/CT scan. <p><i>Wang P et al. Clin Nucl Med. [PMID: 33351512]</i></p>
RICKETS & OSTEOMALACIA Page 1169	<ul style="list-style-type: none"> For patients with tumoral hypophosphatemia, resection of the tumor normalizes serum phosphate levels, but about 20% experience recurrence, usually in the same location. With both tumoral and genetic fibroblast growth factor 23 (FGF-23)-related hypophosphatemia, therapy with burosomab improves osteomalacia. For patients who cannot take burosomab or who continue to have hypophosphatemia, oral phosphate supplements must be given long-term; oral phosphate causes diarrhea at higher doses, however, so many patients do not achieve normal serum phosphate levels. Calcitriol, 0.25–0.5 mcg daily is given to improve the impaired calcium absorption caused by the oral phosphate. Patients with hypophosphatasia may be treated with asfotase alfa (Strensiq). Teriparatide can improve bone pain and fracture healing. Bisphosphonates are contraindicated. <p><i>Lecoq AL et al. Metabolism. [PMID: 31863781] Insogna KL et al. J Bone Miner Res. [PMID: 31369697]</i></p>
MALE HYPOGONADISM Page 1194	<ul style="list-style-type: none"> An oral preparation of testosterone undecanoate (Jatenzo) is available in capsules of 158 mg, 198 mg, and 237 mg and should be taken with food. Serum testosterone falls to low levels by 12 hours after an oral dose; dosing every 8 hours may produce more consistent serum testosterone levels. <p><i>Swerdloff RS et al. J Clin Endocrinol Metab. [PMID: 32382745]</i></p>
MALE HYPOGONADISM Page 1194	<ul style="list-style-type: none"> Testosterone replacement has not been considered to significantly increase the risk of thromboembolic events in most hypogonadal men. However, one large medical database study has found a correlation between testosterone therapy and thromboembolic events, particularly in men with a prior history of vascular events and in men being prescribed testosterone without proper documentation of hypogonadism. <p><i>Walker RF et al. JAMA Intern Med. [PMID: 31710339]</i></p>
DIABETES MELLITUS Page 1228	<ul style="list-style-type: none"> Dapagliflozin reduced the risk of end-stage kidney disease or death from renal and cardiovascular causes in a 2020 multinational study of 4304 patients with chronic kidney disease. The drug was safe and beneficial in patients with estimated glomerular filtration rate as low as 25 mL/min/1.73 m². A third of the patients in the study did not have diabetes and had benefit. <p><i>Heerspink HJL et al. N Engl J Med. [PMID: 32970396]</i></p>
TREATMENT OF HIGH LDL CHOLESTEROL Page 1264	<ul style="list-style-type: none"> There remains controversy about the efficacy of omega-3 therapies, since the 2020 STRENGTH trial showed no cardiovascular disease benefit of omega-3 carboxylic acids; it remains unclear if this result was due to a different omega-3 fatty acid preparation, chance, or a much smaller benefit of omega-3 fatty acids preparations than originally demonstrated. <p><i>Nicholls SJ et al. JAMA. [PMID: 33190147]</i></p>
TREATMENT OF HIGH LDL CHOLESTEROL Page 1264	<ul style="list-style-type: none"> Bempedoic acid lowers low-density lipoprotein (LDL) approximately 17–20% on top of moderate to high intensity statins. Similar to statins, bempedoic acid targets cholesterol synthesis in the liver; bempedoic acid inhibits adenosine triphosphate citrate lyase, an enzyme that is upstream of the mechanism of statins (inhibition of HMG-CoA reductase). Bempedoic acid is also marketed in combination with ezetimibe; this combination provides approximately 38% LDL reduction on top of background lipid-lowering therapy. Treatment with bempedoic acid may mildly decrease both high sensitivity C-reactive protein (hsCRP) and the risk of diabetes. Bempedoic acid also appears to modestly increase the risk of tendon rupture. Bempedoic acid should not be used with more than 20 mg of simvastatin daily or 40 mg of pravastatin daily. <p><i>Di Minno A et al. J Am Heart Assoc. [PMID: 32689862]</i></p>

*See chapter for further details and references.

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Topic	New Advances Affecting Clinical Practice*
OBESITY Page 1274	<ul style="list-style-type: none"> The five FDA-approved devices for the treatment of obesity include two intragastric balloons (Orbera and Obalon), the AspireAssist aspiration device, superabsorbent hydrogel capsules (Plenity), and the TransPyloric Shuttle device. <p>Tchang BG et al. <i>Med Clin North Am.</i> [PMID: 33246516]</p>
OBESITY Page 1274	<ul style="list-style-type: none"> The endoscopic sleeve gastroplasty is a newer option for surgical treatment of obesity that has gained popularity. It uses an endoscopic suturing device to reduce the cavity of the stomach, mimicking the surgical sleeve gastrectomy without the need for surgical resection. <p>Hedjoudje A et al. <i>Clin Gastroenterol Hepatol.</i> [PMID: 31442601]</p>
HIV & AIDS Page 1368	<ul style="list-style-type: none"> Cabotegravir is an integrase inhibitor that has been approved for use in the United States, Canada, and in the European Union. It is intended to be given with rilpivirine. The advantage of this combination is that it is complete therapy for patients in whom the viral load is stable and suppressed (< 50 copies) on their current regimen, which is then stopped in favor of cabotegravir/rilpivirine. <p>Swindells S et al. <i>N Engl J Med.</i> [PMID: 32130809]</p>
HIV & AIDS Page 1372	<ul style="list-style-type: none"> Fostemsavir, an attachment inhibitor, and ibalizumab, a monoclonal antibody, are FDA approved specifically for heavily treated adults with multidrug-resistant HIV who are not responding to their existing regimen. <p>Kozal M et al. <i>N Engl J Med.</i> [PMID: 32212519]</p>
SEVERE ACUTE RESPIRATORY SYNDROME—CORONAVIRUS 2019 (SARS-CoV-2) Page 1422	<ul style="list-style-type: none"> CMDT updates the ever-evolving knowledge of SARS-CoV-2 and the related disease online at www.accessmedicine.com.
BRONCHOGENIC CARCINOMA Page 1626	<ul style="list-style-type: none"> ROS1-rearranged lung cancers respond to crizotinib (ALK, cMET, and ROS1 tyrosine kinase inhibitor) and entrectinib (multikinase inhibitor, including ROS-1) with response rates over 70%. <p>Dirlon A et al. <i>Lancet Oncol.</i> [PMID: 31838015]</p>
BRONCHOGENIC CARCINOMA Page 1626	<ul style="list-style-type: none"> For patients whose non-small cell lung cancer (NSCLC) reveals NTRK 1/2/3 gene fusion, treatment with larotrectinib (TRKA/B/C inhibitor) or entrectinib (multikinase inhibitor, including TRKA/B/C) is recommended. Selpercatinib and pralsetinib (RET inhibitors) are recommended first-line treatments for RET fusion-positive NSCLC. <p>Dirlon A et al. <i>Lancet Oncol.</i> [PMID: 31838015]</p>
HEPATOCELLULAR CARCINOMA Page 1631	<ul style="list-style-type: none"> The combination of atezolizumab, an immune checkpoint inhibitor, and bevacizumab, an antibody to the vascular endothelial growth factor receptor, has been shown to be superior to sorafenib and is now standard first-line therapy. <p>Bangaru S et al. <i>Aliment Pharmacol Ther.</i> [PMID: 31747082]</p>
HEPATOCELLULAR CARCINOMA Page 1631	<ul style="list-style-type: none"> The combination of nivolumab and ipilimumab has been recommended as second-line therapy after failure of sorafenib. <p>Bangaru S et al. <i>Aliment Pharmacol Ther.</i> [PMID: 31747082]</p>
MALIGNANT EFFUSIONS Page 1667	<ul style="list-style-type: none"> In a meta-analysis of randomized controlled trials comparing indwelling pleural catheter with pleurodesis for malignant pleural effusions, indwelling pleural catheters resulted in shorter hospital stays and fewer repeat pleural interventions but increased rates of cellulitis. <p>Iyer NP et al. <i>Ann Am Thorac Soc.</i> [PMID: 30272486]</p>
HYPERURICEMIA & TUMOR LYSIS SYNDROME Page 1669	<ul style="list-style-type: none"> It is recommended to maintain a urinary output of at least 100 mL/hour, and a daily urine volume of at least 3 L/day. If evidence of volume overload or inadequate urinary output develop, loop diuretics can be used. Thiazide diuretics are contraindicated because they increase uric acid levels and can interact with allopurinol. <p>Matuszkiewicz-Rowinska J et al. <i>Kidney Blood Press Res.</i> [PMID: 32998135]</p>

*See chapter for further details and references.

Topic	New Advances Affecting Clinical Practice *
LOW BACK PAIN Page 1695	<ul style="list-style-type: none"> Exercise, oral NSAIDs, and serotonin and norepinephrine reuptake inhibitors (duloxetine) were shown in a systematic review to produce a clinically meaningful reduction in pain, with exercise being the only intervention that demonstrated sustained benefit after the intervention ended. <i>Kolber MR et al. Can Fam Physician. [PMID: 33483410]</i>
SPINAL STENOSIS Page 1696	<ul style="list-style-type: none"> A 2021 meta-analysis comparing fusion and nonfusion surgeries for lumbar spinal stenosis found no difference in clinical effects and complications, highlighting the challenge of surgical intervention for lumbar spinal stenosis. <i>Shen J et al. Adv Ther. [PMID: 33491158]</i>
LUMBAR DISK HERNIATION Page 1697	<ul style="list-style-type: none"> A 2020 Cochrane review of 25 placebo-controlled trials provides moderate-quality evidence that epidural corticosteroid injections are effective, although the treatment effects are small (mean difference < 10%) and short-term for improving radicular pain for individuals. There is level I evidence for the use of transforaminal injections for radicular pain from disk herniation. <i>Oliveira CB et al. Cochrane Database Syst Rev. [PMID: 32271952]</i>
KNEE OSTEOARTHRITIS Page 1715	<ul style="list-style-type: none"> The first-line recommendation for pain management is topical nonsteroidal medication. Alternatively, topical capsaicin may be effective. Acetaminophen has been shown to be less effective than NSAIDs but can be used in patients when NSAID use is contraindicated. Tramadol can be used appropriately in patients with severe osteoarthritis as alternative to NSAIDs, while opioid use is discouraged. <p><i>Sharma L. N Engl J Med. [PMID: 33406330]</i></p>
HEALTH DISPARITIES & THE MINORITY STRESS MODEL Page 1721	<ul style="list-style-type: none"> The SARS-CoV-2 pandemic most likely has disproportionately affected the sexual gender minority (SGM) community; sexual orientation and gender identity data, however, were not considered in reporting prevalence or outcomes. One study documented that coincident with the pandemic, there is increased depression and anxiety within the SGM community in persons who did not have preexisting anxiety or depression. <i>Flentje A, Obedin-Maliver J et al. J Gen Intern Med. [PMID: 32556877]</i>
FAMILY PLANNING Page 1723	<ul style="list-style-type: none"> A recent study evaluated pregnancy termination for transgender, nonbinary, and gender expansive people and found that the majority preferred medication abortion due to their belief that it was the least invasive, although the majority of the respondents had undergone a surgical abortion. <i>Moseson H et al. Am J Obstet Gynecol. [PMID: 32986990]</i>
ANTIVIRAL CHEMOTHERAPY Part e1-24	<ul style="list-style-type: none"> Remdesivir is approved for the treatment of SARS-CoV-2 in hospitalized patients. In a multinational, randomized trial, hospitalized patients infected with SARS-CoV-2 who received remdesivir showed a significant reduction in the time to recovery compared to those who received placebo; those requiring supplemental oxygen benefited the most from remdesivir treatment. <i>Beigel JH et al. N Engl J Med. [PMID: 32445440]</i>
TELEMEDICINE Part e3-09	<ul style="list-style-type: none"> The SARS-CoV-2 pandemic has produced an explosion in the use of telehealth. In the United States, video visits that had previously not been reimbursed by government-sponsored payment programs became reimbursable. In addition to the obvious need to be "in person" for a phlebotomy, electrocardiogram, or other procedure, concerns have arisen about whether some diagnostic testing (eg, cancer screening) or another vital health care maintenance procedure (eg, scheduled vaccination) may now be underutilized because it is now comparatively inconvenient. Other aspects of practice management, such as completion of forms, scheduling, and follow-up, are being moved to "virtual" platforms, which will gradually make remote care more complete and sustainable. It remains to be seen whether the changes to policy and to reimbursement implemented during the pandemic will be reversed with return to a post-pandemic "new normal" or will be made permanent, <i>Kichloo A et al. Fam Med Community Health. [PMID: 32816942]</i>
MEDITATION Part e4-07	<ul style="list-style-type: none"> A 2020 meta-analysis over 3000 patients found that mindfulness-based interventions were associated reductions in anxiety for at least 6 months after the intervention in adults with a cancer diagnosis. <i>Oberoi S et al. JAMA Netw Open. [PMID: 32766801]</i>
TAI CHI Part e4-12	<ul style="list-style-type: none"> A 2020 review synthesized evidence from more than 200 meta-analyses of randomized controlled trials with over 100 unique health outcomes found evidence supporting tai chi in the improvement of physical and mental health among adults with cancer, neurological disorders such as Parkinson disease, metabolic diseases, cardiopulmonary diseases including heart failure and coronary artery disease, musculoskeletal diseases such as fibromyalgia, and psychological disorders. <i>Zou L et al. Am J Med. [PMID: 32946848]</i>

*See chapter for further details and references.

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Topic	New Advances Affecting Clinical Practice*
CHRONIC PELVIC PAIN IN WOMEN Part e6-13	<ul style="list-style-type: none"> A large, randomized controlled trial of women with chronic pelvic pain demonstrated that side effects of gabapentin—dizziness, drowsiness, and visual disturbances—were common while pain control in the gabapentin group was no better than in the placebo group. <i>Horne AW et al; GaPP2 collaborative. Lancet. [PMID: 32979978]</i>
ASYMPTOMATIC OVARIAN MASSES Part e6-16	<ul style="list-style-type: none"> In 2020, the American College of Radiology developed the Ovarian-Adnexal Reporting and Data System (O-RADS), which applied the International Ovarian Tumor Analysis criteria to standardize the reporting of ovarian findings in US imaging reports and the process of communicating risk of malignancy to providers. <i>Stein EB et al. Abdom Radiol (NY). [PMID: 33079254]</i>

ANCA, antineutrophil cytoplasmic antibodies; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.