11 - Infectious Diseases

Chapter 129. Biology of Infectious Disease

Introduction

A healthy person lives in harmony with the microbial flora that helps protect its host from invasion by pathogens, usually defined as microorganisms that have the capacity to cause disease. The microbial flora is mostly bacteria and fungi and includes normal resident flora, which is present consistently and promptly reestablishes itself if disturbed, and transient flora, which may colonize the host for hours to weeks but does not permanently establish itself. Organisms that are normal flora can occasionally cause disease, especially when defenses are disrupted.

Tropisms (attractions to certain tissues) determine which body sites microorganisms colonize. Normal flora is influenced by tropisms and many other factors (eg, diet, hygiene, sanitary conditions, air pollution). For example, lactobacilli are common in the intestines of people with a high intake of dairy products; *Haemophilus influenzae* colonizes the tracheobronchial tree in patients with COPD.

Host Defense Mechanisms

Host defenses that protect against infection include natural barriers (eg, skin, mucous membranes), nonspecific immune responses (eg, phagocytic cells [neutrophils, macrophages] and their products), and specific immune responses (eg, antibodies, lymphocytes).

Natural Barriers

Skin: The skin usually bars invading microorganisms unless it is physically disrupted (eg, by injury, IV catheter, or surgical incision). Exceptions include human papillomavirus, which can invade normal skin, causing warts, and some parasites (eg, *Schistosoma mansoni*, *Strongyloides stercoralis*).

Mucous membranes: Many mucous membranes are bathed in secretions that have antimicrobial properties (eg, cervical mucus, prostatic fluid, and tears containing lysozyme, which splits the muramic acid linkage in bacterial cell walls, especially in gram-positive organisms). Local secretions also contain immunoglobulins, principally IgG and secretory IgA, which prevent microorganisms from attaching to host cells.

Respiratory tract: The respiratory tract has upper airway filters. If invading organisms reach the tracheobronchial tree, the mucociliary epithelium transports them away from the lung. Coughing also helps remove organisms. If the organisms reach the alveoli, alveolar macrophages and tissue histiocytes engulf them. However, these defenses can be overcome by large numbers of organisms or by compromised effectiveness resulting from air pollutants (eg, cigarette smoke) or interference with protective mechanisms (eg, endotracheal intubation, tracheostomy).

GI tract: GI tract barriers include the acid pH of the stomach and the antibacterial activity of pancreatic enzymes, bile, and intestinal secretions. Peristalsis and the normal loss of epithelial cells remove microorganisms. If peristalsis is slowed (eg, because of drugs such as belladonna or opium alkaloids), this removal is delayed and prolongs some infections, such as symptomatic shigellosis. Compromised GI defense mechanisms may predispose patients to particular infections (eg, achlorhydria predisposes to salmonellosis). Normal bowel flora can inhibit pathogens; alteration of this flora with antibiotics can allow overgrowth of inherently pathogenic microorganisms (eg, *Salmonella typhimurium*) or superinfection with ordinarily commensal organisms (eg, *Candida albicans*).

GU tract: GU tract barriers include the length of the urethra (20 cm) in men, the acid pH of the vagina in women, and the hypertonic state of the kidney medulla. The kidneys also produce and excrete large amounts of Tamm-Horsfall mucoprotein, which binds certain bacteria, facilitating their harmless excretion.

Nonspecific Immune Responses

Cytokines (including IL-1, IL-6, tumor necrosis factor, interferon-γ) are produced principally by macrophages and activated lymphocytes and mediate an acute-phase response that develops regardless of the inciting microorganism (see also p.). The response involves fever and increased production of neutrophils by the bone marrow. Endothelial cells also produce large amounts of IL-8, which attracts neutrophils.

The inflammatory response directs immune system components to injury or infection sites and is manifested by increased blood supply and vascular permeability, which allows chemotactic peptides, neutrophils, and mononuclear cells to leave the intravascular compartment. Microbial spread is limited by engulfment of microorganisms by phagocytes (eg, neutrophils, macrophages). Phagocytes are drawn to microbes via chemotaxis and engulf them, releasing phagocytic lysosomal contents that help destroy microbes. Oxidative products such as hydrogen peroxide are generated by the phagocytes and kill ingested microbes. When quantitative or qualitative defects in neutrophils result in infection, the infection is usually prolonged and recurrent and responds slowly to antimicrobial drugs. Staphylococci, gram-negative organisms, and fungi are the pathogens usually responsible.

Specific Immune Responses

After infection, the host can produce a variety of antibodies, complex glycoproteins known as immunoglobulins that bind to specific microbial antigenic targets. Antibodies can help eradicate the infecting organism by attracting the host's WBCs and activating the complement system. The complement system (see p.) destroys cell walls, usually through the classic pathway. Complement can also be activated on the surface of some microorganisms via the alternative pathway. Antibodies can also promote the deposition of substances known as opsonins (eg, the complement protein C3b) on the surface of microorganisms, which helps promote phagocytosis. Opsonization is important for eradication of encapsulated organisms such as pneumococci and meningococci.

Factors Facilitating Microbial Invasion

Microbial invasion can be facilitated by virulence factors, microbial adherence, resistance to antimicrobials, and defects in host defense mechanisms.

Virulence Factors

Virulence factors assist pathogens in invasion and resistance of host defenses; these factors include

• Capsules

• Enzymes

• Toxins

Capsules: Some organisms (eg, certain strains of pneumococci, meningococci, type B *Haemophilus influenzae*) have capsules that prevent opsonic antibodies from binding and thus are more virulent than nonencapsulated strains.

Enzymes: Bacterial proteins with enzymatic activity (eg, protease, hyaluronidase, neuraminidase, elastase, collagenase) facilitate local tissue spread. Invasive organisms (eg, *Shigella flexneri*, *Yersinia enterocolitica*) can penetrate and traverse intact eukaryotic cells, facilitating entry from mucosal surfaces.

Some bacteria (eg, *Neisseria gonorrhoeae*, *H. influenzae*, *Proteus mirabilis*, clostridial species, *Streptococcus pneumoniae*) produce IgA-specific proteases that cleave and inactivate secretory IgA on mucosal surfaces.

Toxins: Organisms may release toxins (called exotoxins), which are protein molecules that may cause the disease (eg, diphtheria, cholera, tetanus, botulism) or increase the severity of the disease. Most toxins bind to specific target cell receptors. With the exception of preformed toxins responsible for food-borne

illnesses, toxins are produced by organisms during the course of infection.

Endotoxin is a lipopolysaccharide produced by gram-negative bacteria and is part of the cell wall. Endotoxin triggers humoral enzymatic mechanisms involving the complement, clotting, fibrinolytic, and kinin pathways and causes much of the morbidity in gram-negative sepsis.

Other factors: Many microorganisms have mechanisms that impair antibody production by inducing suppressor cells, blocking antigen processing, and inhibiting lymphocyte mitogenesis.

Resistance to the lytic effects of serum complement confers virulence. Among species of *N. gonorrhoeae*, resistance predisposes to disseminated rather than localized infection.

Some organisms resist the oxidative steps in phagocytosis. For example, *Legionella* and *Listeria* either do not elicit or actively suppress the oxidative step, whereas other organisms produce enzymes (eg, catalase, glutathione reductase, or superoxide dismutase) that mitigate the oxidative products.

Microbial Adherence

Adherence to surfaces helps microorganisms establish a base from which to penetrate tissues. Among the factors that determine adherence are adhesins (microbial molecules that mediate attachment to a cell) and host receptors to which the adhesins bind. Host receptors include cell surface sugar residues and cell surface proteins (eg, fibronectin) that enhance binding of certain gram-positive organisms (eg, staphylococci). Other determinants of adherence include fine structures on certain bacterial cells (eg, streptococci) called fibrillae, by which some bacteria bind to human epithelial cells. Other bacteria, such as Enterobacteriaceae (eg, *Escherichia coli*), have specific adhesive organelles called fimbriae or pili. Fimbriae enable the organism to attach to almost all human cells, including neutrophils and epithelial cells in the GU tract, mouth, and intestine.

Biofilm: Biofilm is a slime layer that can form around certain bacteria and confer resistance to phagocytosis and antibiotics. It develops around *Pseudomonas aeruginosa* in the lungs of patients with cystic fibrosis and around coagulase-negative staphylococci on synthetic medical devices, such as IV catheters, prosthetic vascular grafts, and suture material. Factors that affect the likelihood of biofilm developing on such medical devices include the material's roughness, chemical composition, and hydrophobicity.

Antimicrobial Resistance

Genetic variability among microbes is inevitable. Use of antimicrobial drugs eventually selects for survival of strains that are capable of resisting them.

In many cases, resistant bacterial strains have acquired genes that are encoded on plasmids or transposons and that enable the microorganisms to synthesize enzymes that

• Modify or inactivate the antimicrobial agent

• Change the bacterial cell's ability to accumulate the antimicrobial agent

• Resist inhibition by the antimicrobial agent

Minimizing inappropriate use of antibiotics is important for public health. Resistance among bacteria is discussed on p. .

Defects in Host Defense Mechanisms

Two types of immune deficiency states affect the host's ability to fight infection: Primary immune deficiency and secondary (acquired) immune deficiency.

Primary immune deficiencies are genetic in origin; > 100 primary immune deficiency states have been

described. Most primary immune deficiencies are recognized during infancy; however, up to 40% are recognized during adolescence or adulthood.

Acquired immune deficiencies are caused by another disease (eg, cancer, HIV infection, chronic disease) or by exposure to a chemical or drug that is toxic to the immune system.

Mechanisms: Defects in immune responses may involve

• Cellular immunity

• Humoral immunity

• Phagocytic system

• Complement system

Cellular deficiencies are typically T-cell or combined immune defects. T cells contribute to the killing of intracellular organisms; thus, patients with T-cell defects can present with opportunistic infections such as *Pneumocystis jirovecii* or cryptococcal infections. Chronicity of these infections can lead to failure to thrive, chronic diarrhea, and persistent oral candidiasis.

Humoral deficiencies are typically caused by the failure of B cells to make functioning immunoglobulins. Patients with this type of defect usually have infections involving encapsulated organisms (eg, *H. influenzae*, streptococci). Patients can present with poor growth, diarrhea, and recurrent sinopulmonary infections.

A defect in the phagocytic system affects the immediate immune response to bacterial infection and can result in development of recurrent abscesses, severe pneumonias, or delayed umbilical cord separation.

Primary complement system defects are particularly rare. Patients with this type of defect may present with recurrent infections with pyogenic bacteria (eg, encapsulated bacteria, *Neisseria* sp) and have an increased risk of autoimmune disorders (eg, SLE).

Manifestations of Infection

Manifestations may be local (eg, cellulitis, abscess) or systemic, most often fever (see p. 1152). Manifestations may develop in multiple organ systems. Severe, generalized infections may have life-threatening manifestations (eg, sepsis, septic shock—see p. 2299). Most manifestations resolve with successful treatment of the underlying infection.

Clinical: Most infections increase the pulse rate and body temperature, but others (eg, typhoid fever, tularemia, brucellosis, dengue) may not elevate the pulse rate commensurate with the degree of fever. Hypotension can result from hypovolemia or septic shock. Hyperventilation and respiratory alkalosis are common.

Alterations in sensorium (encephalopathy) may occur in severe infection regardless of whether CNS infection is present. Encephalopathy is most common and serious in the elderly and may cause anxiety, confusion, delirium, stupor, seizures, and coma.

Hematologic: Infectious diseases commonly increase the numbers of mature and immature circulating neutrophils. Mechanisms include demargination and release of immature granulocytes from bone marrow, IL-1- and IL-6-mediated release of neutrophils from bone marrow, and colony-stimulating factors elaborated by macrophages, lymphocytes, and other tissues. Exaggeration of these phenomena (eg, in trauma, inflammation, and similar stresses) can result in release of excessive numbers of immature leukocytes into the circulation (leukemoid reaction), with leukocyte counts up to 25 to 30 × 10^9/L.

Conversely, some infections (eg, typhoid fever, brucellosis) commonly cause neutropenia. In

overwhelming, severe infections, profound neutropenia is often a poor prognostic sign. Characteristic morphologic changes in the neutrophils of septic patients include Dohle bodies, toxic granulations, and vacuolization.

Anemia can develop despite adequate tissue iron stores. If anemia is chronic, plasma iron and total iron-binding capacity may be decreased. Serious infection, particularly with gram-negative organisms, may cause disseminated intravascular coagulation (DIC—see p.).

Other organ systems: Pulmonary compliance may decrease, progressing to acute respiratory distress syndrome (ARDS) and respiratory muscle failure.

Renal manifestations range from minimal proteinuria to acute renal failure, which can result from shock and acute tubular necrosis, glomerulonephritis, or tubulointerstitial disease.

Hepatic dysfunction, including cholestatic jaundice (often a poor prognostic sign) or hepatocellular dysfunction, occurs with many infections, even though the infection does not localize to the liver. Upper GI bleeding due to stress ulceration may occur during sepsis.

Endocrinologic dysfunctions include increased production of thyroid-stimulating hormone, vasopressin, insulin, and glucagon; breakdown of skeletal muscle proteins and muscle wasting secondary to increased metabolic demands; and bone demineralization. Hypoglycemia occurs infrequently in sepsis, but adrenal insufficiency should be considered in patients with hypoglycemia and sepsis. Hyperglycemia may be an early sign of infection in diabetics.

Fever

Fever is elevated body temperature (> 37.8° C orally or > 38.2° C rectally) or an elevation above a person's known normal daily value. Elevated body temperature that is not caused by a resetting of the temperature set point in the hypothalamus is commonly called hyperthermia. Many patients use "fever" very loosely, often meaning that they feel too warm, too cold, or sweaty, but they have not actually measured their temperature.

Symptoms are due mainly to the condition causing the fever, although fever itself can cause discomfort.

Pathophysiology

During a 24-h period, temperature varies from lowest levels in the early morning to highest in late afternoon. Maximum variation is about 0.6° C.

Body temperature is determined by the balance between heat production by tissues, particularly the liver and muscles, and heat loss from the periphery. Normally, the hypothalamic thermoregulatory center maintains the internal temperature between 37° and 38° C. Fever results when something raises the hypothalamic set point, triggering vasoconstriction and shunting of blood from the periphery to decrease heat loss; sometimes shivering, which increases heat production, is induced. These processes continue until the temperature of the blood bathing the hypothalamus reaches the new set point. Resetting the hypothalamic set point downward (eg, with antipyretic drugs) initiates heat loss through sweating and vasodilation. The capacity to generate a fever is reduced in certain patients (eg, alcoholics, the very old, the very young).

Pyrogens are substances that cause fever. Exogenous pyrogens are usually microbes or their products. The best studied are the lipopolysaccharides of gram-negative bacteria (commonly called endotoxins) and *Staphylococcus aureus* toxin, which causes toxic shock syndrome. Exogenous pyrogens usually cause fever by inducing release of endogenous pyrogens (eg, IL-1, tumor necrosis factor [TNF], interferon-γ, IL-6), which raise the hypothalamic set point. Prostaglandin E_2 synthesis appears to play a critical role.

Consequences of fever: Although many patients worry that fever itself can cause harm, the modest transient core temperature elevations (ie, 38° to 40°) caused by most acute illnesses are well tolerated by

healthy adults. However, extreme temperature elevation (typically > 41° C) may be damaging. Such elevation is more typical of severe environmental hyperthermia but sometimes results from exposure to illicit drugs (eg, cocaine, phencyclidine), anesthetics, or antipsychotic drugs. At this temperature, protein denaturation occurs, and inflammatory cytokines that activate the inflammatory cascade are released. As a result, cellular dysfunction occurs, leading to malfunction and ultimately failure of most organs; the coagulation cascade is also activated, leading to disseminated intravascular coagulation.

Because fever can increase the BMR by about 10 to 12% for every 1° C increase over 37° C, fever may physiologically stress adults with preexisting cardiac or pulmonary insufficiency. Fever can also worsen mental status in patients with dementia.

Fever in healthy children can cause febrile seizures (see p.).

Etiology

Many disorders can cause fever. They are broadly categorized as

• Infectious (most common)

• Neoplastic

• Inflammatory (including rheumatic, nonrheumatic, and drug-related)

The cause of an acute (ie, duration ≤ 4 days) fever in adults is highly likely to be infectious. When patients present with fever due to a noninfectious cause, the fever is almost always chronic or recurrent. Also, an isolated, acute febrile event in patients with a known inflammatory or neoplastic disorder is still most likely to be infectious. In healthy people, an acute febrile event is unlikely to be the initial manifestation of a chronic illness.

Infectious causes: Virtually all infectious illnesses can cause fever. But overall, the most likely causes are

• Upper and lower respiratory tract infections

• GI infections

• UTIs

• Skin infections

Most acute respiratory tract and GI infections are viral.

Specific patient and external factors also influence which causes are most likely.

Patient factors include health status, age, occupation, and risk factors (eg, hospitalization, recent invasive procedures, presence of IV or urinary catheters, use of mechanical ventilation).

External factors are those that expose patients to specific diseases—eg, through infected contacts, local outbreaks, disease vectors (eg, mosquitoes, ticks), a common vehicle (eg, food, water), or geographic location (eg, residence in or recent travel to an endemic area).

Some causes appear to predominate based on these factors (see).

Evaluation

Two general issues are important in the initial evaluation of acute fever:

• Identifying any localizing symptoms (eg, headache, cough): These symptoms help narrow the range of possible causes. The localizing symptom may be part of the patient's chief complaint or identified only by specific questioning.

• Determining whether the patient is seriously or chronically ill (particularly if such illness is unrecognized): Many causes of fever in healthy people are self-limited, and many of the possible viral infections are difficult to diagnose specifically. Limiting testing to the seriously or chronically ill can help avoid many expensive, unnecessary, and often fruitless searches.

History: History of present illness should cover magnitude and duration of fever and method used to take the temperature. True rigors (severe, shaking, teeth-chattering chills—not simply feeling cold) suggest fever due to infection but are not otherwise specific. Pain is an important clue to the possible source; the patient should be asked about pain in the ears, head, neck, teeth, throat, chest, abdomen, flank, rectum, muscles, and joints.

Other localizing symptoms include nasal congestion and/or discharge, cough, diarrhea, and urinary symptoms (frequency, urgency, dysuria). Presence of rash (including nature, location, and time of onset in relation to other symptoms) and lymphadenopathy may help. Infected contacts and their diagnosis should be identified.

Review of systems should identify symptoms of chronic illness, including recurrent fevers, night sweats, and weight loss.

Past medical history should particularly cover the following:

• Recent surgery

• Known disorders that predispose to infection (eg, HIV infection, diabetes, cancer, organ transplantation, sickle cell disease, valvular heart disorders—particularly if an artificial valve is present)

• Other known disorders that predispose to fever (eg, rheumatologic disorders, SLE, gout, sarcoidosis, hyperthyroidism, cancer)

Questions to ask about recent travel include location, time since return, locale (eg, in back country, only in cities), vaccinations received before travel, and any use of prophylactic antimalarial drugs (if required).

All patients should be asked about possible exposures (eg, via unsafe food or water, insect bites, animal contact, or unprotected sex).

Vaccination history, particularly against hepatitis A and B and against organisms that cause meningitis, influenza, or pneumococcal infection, should be noted.

Drug history should include specific questions about the following:

• Drugs known to cause fever (see Table 129-1)

• Drugs that predispose to infection (eg, corticosteroids, anti-TNF drugs, chemotherapeutic and antirejection drugs, other immunosuppressants)

• Illicit use of injection drugs (predisposing to endocarditis, hepatitis, septic pulmonary emboli, and skin and soft-tissue infections)

Physical examination: Physical examination begins with confirmation of fever. Fever is most accurately diagnosed by measuring rectal temperature. Oral temperatures are normally about 0.6° C lower and may be falsely even lower for many reasons, such as recent ingestion of a cold drink, mouth breathing, hyperventilation, and inadequate measurement time (up to several minutes are required with mercury thermometers). Measurement

[**Table 129-1.** Some Causes of Acute Fever]

of tympanic membrane temperature by infrared sensor is less accurate than rectal temperature.

Other vital signs are reviewed for presence of tachypnea, tachycardia, or hypotension.

For patients with localizing symptoms, examination proceeds as discussed elsewhere in THE MANUAL. For febrile patients without localizing symptoms, a complete examination is necessary because clues to the diagnosis may be in any organ system.

The patient's general appearance, including any weakness, lethargy, confusion, cachexia, and distress, should be noted.

All of the skin should be inspected for rash, particularly petechial or hemorrhagic rash and any lesions or areas of erythema or blistering suggesting skin or soft-tissue infection. Axillae and epitrochlear and inguinal areas should be examined for adenopathy. In hospitalized patients, presence of any IVs, NGTs, urinary catheters, and any other tubes or lines inserted into the body should be noted. If patients have had recent surgery, surgical sites should be thoroughly inspected.

For the head and neck examination, the following should be done:

• Tympanic membranes: Examined for infection

• Sinuses (frontal and maxillary): Percussed

• Temporal arteries: Palpated for tenderness

• Nose: Inspected for congestion and discharge (clear or purulent)

• Eyes: Inspected for conjunctivitis or icterus

• Fundi: Inspected for Roth's spots (suggesting endocarditis)

• Oropharynx and gingiva: Inspected for inflammation or ulceration (including any lesions of candidiasis, which suggests immunocompromise)

• Neck: Flexed to detect discomfort, stiffness, or both, indicating meningismus, and palpated for adenopathy

The lungs are examined for crackles or signs of consolidation, and the heart is auscultated for murmurs (suggesting possible endocarditis).

The abdomen is palpated for hepatosplenomegaly and tenderness (suggesting infection).

The flanks are percussed for tenderness over the kidneys (suggesting pyelonephritis). A pelvic examination is done in women to check for cervical motion or adnexal tenderness; a genital examination is done in men to check for urethral discharge and local tenderness.

The rectum is examined for tenderness and swelling, suggesting perirectal abscess (which may be occult in immunosuppressed patients).

All major joints are examined for swelling, erythema, and tenderness (suggesting a joint infection or rheumatologic disorder). The hands and feet are inspected for signs of endocarditis, including splinter hemorrhages under the nails, painful erythematous subcutaneous nodules on the tips of digits (Osler's nodes), and nontender hemorrhagic macules on the palms or soles (Janeway lesions).

Red flags: The following findings are of particular concern:

• Altered mental status

• Headache, stiff neck, or both

• Petechial skin rash

• Hypotension

• Significant tachycardia or tachypnea

• Temperature > 40° C or < 35° C

• Recent travel to malaria-endemic area

• Recent use of immunosuppressants

Interpretation of findings: The degree of elevation in temperature usually does not predict the likelihood or cause of infection. Fever pattern, once thought to be significant, is not.

Likelihood of serious illness is considered. If serious illness is suspected, immediate and aggressive testing and often hospital admission are needed.

Red flag findings strongly suggest a serious disorder. Headache, stiff neck, and petechial or purpuric rash suggest meningitis. Tachycardia (beyond the modest elevation normally present with fever) and tachypnea, with or without hypotension or mental status changes, suggest sepsis. Malaria should be suspected in patients who have recently traveled to an endemic area.

Immunocompromise, whether caused by a known disorder or use of immunosuppressants or suggested by examination findings (eg, weight loss, oral candidiasis), is also of concern, as are other known chronic illnesses, injection drug use, and heart murmur.

The elderly, particularly those in nursing homes, are at particular risk (see Geriatrics Essentials on p. 1157).

Localizing findings identified by history or physical examination are evaluated and interpreted (see elsewhere in THE MANUAL). Other suggestive findings include generalized adenopathy and rash.

Generalized adenopathy may occur in older children and younger adults who have acute mononucleosis; it is usually accompanied by significant pharyngitis, malaise, and hepatosplenomegaly. Primary HIV infection or secondary syphilis should be suspected in patients with generalized adenopathy, sometimes accompanied by arthralgias, rash, or both. HIV infection develops 2 to 6 wk after exposure (although patients may not always report unprotected sexual contact or other risk factors). Secondary syphilis is usually preceded by a chancre, with systemic symptoms developing 4 to 10 wk later.

Fever and rash have many infectious and drug causes. Petechial or purpuric rash is of particular concern; it suggests possible meningococcemia, Rocky Mountain spotted fever (particularly if the palms or soles are involved), and, less commonly, some viral infections (eg, dengue fever, hemorrhagic fevers). Other suggestive skin lesions include the classic erythema migrans rash of Lyme disease, target lesions of Stevens-Johnson syndrome, and the painful, tender erythema of cellulitis and other bacterial soft-tissue infections. The possibility of delayed drug hypersensitivity (even after long periods of use) should be kept in mind.

If no localizing findings are present, healthy people with acute fever and only nonspecific findings (eg, malaise, generalized aches) most likely have a self-limited viral illness, unless a history of exposure to infected contacts (including a new, unprotected sexual contact), to disease vectors, or in an endemic area (including recent travel) suggests otherwise.

Patients with significant underlying disorders are more likely to have an occult bacterial or parasitic

infection. Injection drug users and patients with a prosthetic heart valve may have endocarditis. Immunocompromised patients are predisposed to infection caused by certain microorganisms (see Table 129-1).

Drug fever (with or without rash) is a diagnosis of exclusion, often requiring a trial of stopping the drug. One difficulty is that if antibiotics are the cause, the illness being treated may also cause fever. Sometimes a clue is that the fever and rash begin after clinical improvement from the initial infection and without worsening or reappearance of the original symptoms (eg, in a patient being treated for pneumonia, fever reappears without cough, dyspnea, or hypoxia).

Testing: Testing depends on whether localized findings are present.

If localizing findings are present, testing is guided by clinical suspicion and findings (see also elsewhere in THE MANUAL), as for the following:

• Mononucleosis or HIV infection: Serologic testing

• Rocky Mountain spotted fever: Biopsy of skin lesions to confirm the diagnosis (acute serologic testing is unhelpful)

• Bacterial or fungal infection: Blood cultures to detect possible bloodstream infections

• Meningitis: Immediate lumbar puncture and IV antibiotics (head CT should be done before lumbar puncture if patients are at risk of brain herniation; IV antibiotics must be given immediately after blood cultures are obtained and before head CT is done)

• Specific disorders based on exposure (eg, to contacts, to vectors, or in endemic areas): Testing for those disorders, particularly a peripheral blood smear for malaria

If no localizing findings are present in otherwise healthy patients and serious illness is not suspected, patients can usually be observed at home without testing. In most, symptoms resolve quickly; the few who develop worrisome or localizing symptoms should be reevaluated and tested based on the new findings.

If serious illness is suspected in patients who have no localizing findings, testing is needed. Patients with red flag findings suggesting sepsis require cultures (urine and blood), chest x-ray, and evaluation for metabolic abnormalities with measurement of serum electrolytes, glucose, BUN, creatinine, lactate, and liver enzymes. CBC is typically done, but sensitivity and specificity for diagnosing serious bacterial infection are low. However, WBC count is important prognostically for patients who may be immunosuppressed (ie, a low WBC count may be associated with a poor prognosis).

Patients with certain underlying disorders may need testing even if they have no localizing findings and do not appear seriously ill. Because of the risk and devastating consequences of endocarditis, febrile injection drug users are usually admitted to the hospital for serial blood cultures and often echocardiography. Patients taking immunosuppressants require CBC; if neutropenia is present, testing is initiated and chest x-ray is done, as are cultures of blood, sputum, urine, stool, and any suspicious skin lesions. Many with neutropenia are admitted to be given IV antibiotics, but certain patients can be sent home provided daily follow-up is available.

Febrile elderly patients often require testing (see Geriatrics Essentials on p. 1157).

Treatment

Specific causes are treated with anti-infective therapy; empiric anti-infective therapy is required when suspicion of serious infection is high.

Whether fever due to infection should be treated is controversial. Experimental evidence, but not clinical studies, suggests that fever enhances host defenses.

Fever should probably be treated in certain patients at particular risk, including adults with cardiac or pulmonary insufficiency or with dementia. Drugs that inhibit brain cyclooxygenase effectively reduce fever:

• Acetaminophen 650 to 1000 mg po q 6 h

• Ibuprofen 400 to 600 mg po q 6 h

The daily dose of acetaminophen should not exceed 4 g to avoid toxicity; patients should be warned not to simultaneously take nonprescription cold or flu remedies that contain acetaminophen. Other NSAIDs (eg, aspirin, naproxen) are also effective antipyretics. Salicylates should not be used to treat fever in children with viral illnesses because use of salicylates has been associated with Reye's syndrome.

If temperature is ≥ 41° C, other cooling measures (eg, evaporative cooling with tepid water mist, cooling blankets) should also be started.

Geriatrics Essentials

In the frail elderly, infection is less likely to cause fever, and even when elevated by infection, temperature may be lower than the standard definition of fever. Similarly, other inflammatory symptoms, such as focal pain, may be less prominent. Frequently, alteration of mental status or decline in daily functioning may be the only other initial manifestations of pneumonia or UTI.

In spite of their less severe manifestations of illness, the febrile elderly are significantly more likely to have a serious bacterial illness than are febrile younger adults. As in younger adults, the cause is commonly a respiratory infection or UTI, but in the elderly, skin and soft-tissue infections are among the top causes.

Focal findings are evaluated as for younger patients. But unlike younger patients, elderly patients probably require urinalysis, urine culture, and chest x-ray. Blood cultures should be done to exclude septicemia; if septicemia is suspected or vital signs are abnormal, patients should be admitted to the hospital.

Key Points

• Most fevers in healthy people are due to viral respiratory tract or GI infections.

• Localizing symptoms guide evaluation.

• Underlying chronic disorders, particularly those impairing the immune system, must be considered.

Fever of Unknown Origin

FUO is body temperature ≥ 38.3° C rectally that does not result from transient and self-limited illness, rapidly fatal illness, or disorders with clear-cut localizing symptoms or signs or with abnormalities on common tests such as chest x-ray, urinalysis, or blood cultures.

FUO is currently classified into 4 distinct categories:

• **Classic FUO:** Fever for ≥ 3 wk with no identified cause after 3 days of hospital evaluation or ≥ 3 outpatient visits

• **Nosocomial FUO:** Fever in hospitalized patients receiving acute care and with no infection present or incubating at admission if the diagnosis remains uncertain after ≥ 3 days of appropriate evaluation, including incubation of microbiologic cultures for ≥ 2 days

• **Neutropenic FUO:** Fever in patients who have < 500 neutrophils/µL or who are expected to have this level within 2 days if the diagnosis remains uncertain after ≥ 3 days of appropriate evaluation, including incubation of microbiologic cultures for ≥ 2 days

- **HIV-associated FUO:** Fever in patients with confirmed HIV infection for > 4 wk as outpatients or > 3 days as inpatients if the diagnosis remains uncertain after ≥ 3 days of appropriate evaluation, including incubation of microbiologic cultures for ≥ 2 days

Etiology

Causes of FUO are usually divided into 4 categories (see Table 129-2):

- Infectious (25 to 50%)

- Connective tissue disorders (10 to 20%)

- Neoplastic (5 to 35%)

- Miscellaneous (15 to 25%)

Infections are the most common cause of FUO. In patients with HIV infection, opportunistic infections (eg, TB; infection by atypical mycobacteria, disseminated fungi, or cytomegalovirus) should be sought.

Common connective tissue disorders include SLE, RA, giant cell arteritis, vasculitis, and juvenile RA of adults.

The most common neoplastic causes are lymphoma, leukemia, renal cell carcinoma, hepatocellular carcinoma, and metastatic carcinomas. However, the incidence of neoplastic causes of FUO has been decreasing, probably because ultrasonography and CT are widely used during initial evaluation.

[**Table 129-2.** Some Causes of FUO]

Important miscellaneous causes include drug reactions, deep venous thrombosis, recurrent pulmonary emboli, sarcoidosis, inflammatory bowel disease, and factitious fever.

No cause of FUO is identified in about 10% of adults.

Evaluation

In puzzling cases, such as FUO, assuming that all information was gathered or was gathered accurately by previous clinicians is usually a mistake. Clinicians should be aware of what patients previously reported (to resolve discrepancies) but should not simply copy details of previously recorded history (eg, family history, social history). Initial errors of omission have been perpetuated through many clinicians over many days of hospitalization, causing much unnecessary testing. Even when initial evaluation was thorough, patients often remember new details when questioning is repeated.

Conversely, clinicians should not ignore previous test results and should not repeat tests without considering how likely results are to be different (eg, because the patient's condition has changed, because a disorder develops slowly).

History: History aims to uncover focal symptoms and facts (eg, travel, occupation, family history, exposure to animal vectors, dietary history) that suggest a cause.

History of present illness should cover duration and pattern (eg, intermittent, constant) of fever. Fever patterns usually have little or no significance in the diagnosis of FUO, although a fever that occurs every other day (tertian) or every 3rd day (quartan) may suggest malaria in patients with risk factors. Focal pain often indicates the location (although not the cause) of the underlying disorder. Clinicians should ask generally, then specifically, about discomfort in each body part.

Review of systems should include nonspecific symptoms, such as weight loss, anorexia, fatigue, night

sweats, and headaches. Also, symptoms of connective tissue disorders (eg, myalgias, arthralgias, rashes) and GI disorders (eg, diarrhea, steatorrhea, abdominal discomfort) should be sought.

Past medical history should include disorders known to cause fever, such as cancer, TB, connective tissue disorders, alcoholic cirrhosis, inflammatory bowel disease, rheumatic fever, and hyperthyroidism. Clinicians should note disorders or factors that predispose to infection, such as immunocompromise (eg, due to disorders such as HIV infection, cancer, diabetes, or use of immunosuppressants), structural heart disorders, urinary tract abnormalities, operations, and insertion of devices (eg, IV lines, pacemakers, joint prostheses).

Drug history should include questions about specific drugs known to cause fever.

Social history should include questions about risk factors for infection such as injection drug use, high-risk sexual practices (eg, unprotected sex, multiple partners), infected contacts (eg, with TB), travel, and possible exposure to animal or insect vectors. Risk factors for cancer, including smoking, alcohol use, and occupational exposure to chemicals, should also be identified.

Family history should include questions about inherited causes of fever (eg, familial Mediterranean fever). Medical records are checked for previous test results, particularly those that effectively rule out certain disorders.

Physical examination: The general appearance, particularly for cachexia, jaundice, and pallor, is noted.

The skin is thoroughly inspected for focal erythema (suggesting a site of infection) and rash (eg, malar rash of SLE); inspection should include the perineum and feet, particularly in diabetics, who are prone to infections in these areas. Clinicians should also check for cutaneous findings of endocarditis, including painful erythematous subcutaneous nodules on the tips of digits (Osler's nodes), nontender hemorrhagic macules on the palms or soles (Janeway lesions), petechiae, and splinter hemorrhages under the nails.

The entire body (particularly over the spine, bones, joints, abdomen, and thyroid) is palpated for areas of tenderness, swelling, or organomegaly; digital rectal examination and pelvic examination are included. The teeth are percussed for tenderness (suggesting apical abscess). During palpation, any regional or systemic adenopathy is noted; eg, regional adenopathy is characteristic of cat-scratch disease in contrast to the diffuse adenopathy of lymphoma.

The heart is auscultated for murmurs (suggesting bacterial endocarditis) and rubs (suggesting pericarditis due to a rheumatologic or infectious disorder).

Sometimes key physical abnormalities in patients with FUO are or seem so subtle that repeated physical examinations may be necessary to suggest causes (eg, by detecting new adenopathy, heart murmurs, rash, or nodularity and weak pulsations in the temporal artery).

Red flags: The following are of particular concern:

• Immunocompromise

• Heart murmur

• Presence of inserted devices (eg, IV lines, pacemakers, joint prostheses)

• Recent travel to endemic areas

Interpretation of findings: After a thorough history and physical examination, the following scenarios are typical:

• Localizing symptoms or signs that were not present, not detected, or not managed during previous examinations are discovered. These findings are interpreted and investigated as indicated (see Table 129-2).

- More commonly, evaluation detects only nonspecific findings that occur in many different causes of FUO, but it identifies risk factors that can help guide testing (eg, travel to an endemic area, exposure to animal vectors). Sometimes risk factors are less specific but may suggest a class of illness; eg, weight loss without anorexia is more consistent with infection than cancer, which usually causes anorexia. Possible causes should be investigated further.

- In the most difficult scenario, patients have only nonspecific findings and no or multiple risk factors, making a logical, sequential approach to testing essential. Initial testing is used to narrow the diagnostic possibilities and guide subsequent testing.

Testing: Previous test results, particularly for cultures, are reviewed. Cultures for some organisms may require a long time to become positive.

As much as possible, clinical information is used to focus testing (see Table 129-2). For example, housebound elderly patients with headache would not be tested for tick-borne infections or malaria, but those disorders should be considered in younger travelers who have hiked in an endemic area. Elderly patients require evaluation for giant cell arteritis; younger patients do not.

In addition to specific testing, the following should usually be done:

- CBC with differential

- ESR

- Liver function tests

- Serial blood cultures (ideally before antimicrobial therapy)

- HIV antibody test, RNA concentration assays, and PCR assay

- Tuberculin skin test

Even if done earlier, these tests may suggest a helpful trend.

Urinalysis, urine culture, and chest x-ray, usually already done, are repeated only if findings indicate that they should be.

Any available fluid or material from abnormal areas identified during the evaluation is cultured (eg, for bacteria, mycobacteria, fungi, viruses, or specific fastidious bacteria as indicated). Organism-specific tests, such as PCR and serologic titers (acute and convalescent), are helpful mainly when guided by clinical suspicion, not done in a shotgun approach.

Serologic tests, such as antinuclear antibody (ANA) and rheumatoid factor, are done to screen for rheumatologic disorders.

Imaging tests are guided by symptoms and signs. Typically, areas of discomfort should be imaged—eg, in patients with back pain, MRI of the spine (to check for infection or tumor); in patients with abdominal pain, CT of the abdomen. However, CT of the chest, abdomen, and pelvis should be considered to check for adenopathy and occult abscesses even when patients do not have localizing symptoms or signs. If blood cultures are positive or new heart murmurs or peripheral signs suggest endocarditis, echocardiography is done.

In general, CT is useful for delineating abnormalities localized to the abdomen or chest. MRI is more sensitive than CT for detecting most causes of FUO involving the CNS and should be done if a CNS cause is being considered. Venous duplex imaging may be useful for identifying cases of deep venous thrombosis. Radionuclide scanning with indium-111-labeled granulocytes may help localize some infectious or inflammatory processes. This technique has generally fallen out of favor because it is

thought to contribute very little to diagnosis, but some reports suggest that it provides a higher diagnostic yield than CT. PET may also be useful in detecting the focus of fever.

Biopsy may be required if an abnormality is suspected in tissue that can be biopsied (eg, liver, bone marrow, skin, pleura, lymph nodes, intestine, muscle). Biopsy specimens should be evaluated by histopathologic examination and cultured for bacteria, fungi, viruses, and mycobacteria or sent for molecular (PCR) diagnostic testing. Muscle biopsy or skin biopsy of rashes may confirm vasculitis. Bilateral temporal artery biopsy may confirm giant cell arteritis in elderly patients with unexplained ESR elevation.

Treatment

Treatment focuses on the causative disorder. Antipyretics should be used judiciously, considering the duration of fever.

Geriatrics Essentials

Causes of FUO in the elderly are usually similar to those in the general population, but connective tissue disorders are identified more often. The most common causes are

• Giant cell arteritis

• Leukemias

• Lymphomas

• Abscesses

• TB

Key Points

• Classic FUO is body temperature ≥ 38.3° C rectally for ≥ 3 wk with no identified cause after 3 days of hospital investigation or ≥ 3 outpatient visits.

• Identified causes can be categorized as infectious, rheumatologic, neoplastic, or miscellaneous.

• Evaluation should be based on synthesis of history and physical examination, with particular consideration of risk factors and likely causes based on individual circumstances.

Abscesses

Abscesses are collections of pus in confined tissue spaces, usually caused by bacterial infection. Symptoms include local pain, tenderness, warmth, and swelling (if abscesses are near the skin layer) or constitutional symptoms (if abscesses are deep). Imaging is often necessary for diagnosis of deep abscesses. Treatment is surgical drainage and often antibiotics.

Etiology

Numerous organisms can cause abscesses, but *Staphylococcus aureus* is the most common. Organisms may enter the tissue by

• Direct implantation (eg, penetrating trauma with a contaminated object)

• Spread from an established, contiguous infection

• Dissemination via lymphatic or hematogenous routes from a distant site

• Migration from a location where there are resident flora into an adjacent, normally sterile area because natural barriers are disrupted (eg, by perforation of an abdominal viscus causing an intra-abdominal abscess)

Abscesses may begin in an area of cellulitis (see p.) or in compromised tissue where leukocytes accumulate. Progressive dissection by pus or necrosis of surrounding cells expands the abscess. Highly vascularized connective tissue may then surround the necrotic tissue, leukocytes, and debris to wall off the abscess and limit further spread.

Predisposing factors to abscess formation include impaired host defense mechanisms (eg, impaired leukocyte defenses), the presence of foreign bodies, obstruction to normal drainage (eg, in the urinary, biliary, or respiratory tracts), tissue ischemia or necrosis, hematoma or excessive fluid accumulation in tissue, and trauma.

Symptoms and Signs

The symptoms and signs of cutaneous and subcutaneous abscesses are pain, heat, swelling, tenderness, and redness. If superficial abscesses are ready to spontaneously rupture, the skin over the center of the abscess may thin, sometimes appearing white or yellow because of the underlying pus (termed pointing). Fever may occur, especially with surrounding cellulitis. For deep abscesses, local pain and tenderness and systemic symptoms, especially fever, as well as anorexia, weight loss, and fatigue are typical. The predominant manifestation of some abscesses is abnormal organ function (eg, hemiplegia due to a brain abscess).

Complications of abscesses include bacteremic spread, rupture into adjacent tissue, bleeding from vessels eroded by inflammation, impaired function of a vital organ, and inanition due to anorexia and increased metabolic needs.

Diagnosis

• Clinical evaluation

• Sometimes ultrasonography or CT

Diagnosis of cutaneous and subcutaneous abscesses is by physical examination. Diagnosis of deep abscesses often requires imaging. Ultrasonography is noninvasive and detects many soft-tissue abscesses; CT is accurate for most, although MRI is usually more sensitive.

Treatment

• Surgical drainage

• Sometimes antibiotics

Superficial abscesses may resolve with heat and oral antibiotics. However, healing usually requires drainage.

Minor cutaneous abscesses may require only incision and drainage. All pus, necrotic tissue, and debris should be removed. Eliminating open (dead) space by packing with gauze or by placing drains may be necessary to prevent reformation of the abscess. Predisposing conditions, such as obstruction of natural drainage or the presence of a foreign body, require correction.

Deep abscesses can sometimes be adequately drained by percutaneous needle aspiration (typically guided by ultrasonography or CT); this method often avoids the need for open surgical drainage.

Spontaneous rupture and drainage may occur, sometimes leading to the formation of chronic draining sinuses. Without drainage, an abscess occasionally resolves slowly after proteolytic digestion of the pus

produces a thin, sterile fluid that is resorbed into the bloodstream. Incomplete resorption may leave a cystic loculation within a fibrous wall that may become calcified.

If the abscess is deep or if there is surrounding cellulitis, systemic antimicrobial drugs are indicated as adjunctive therapy; they are usually ineffective without drainage. Empiric antimicrobial therapy is based on location and likely infecting pathogen. Gram stain, culture, and susceptibility results guide further antimicrobial therapy.

Bacteremia

(See also Neonatal Sepsis on p. and Occult Bacteremia on p. .)

Bacteremia is the presence of bacteria in the bloodstream. It can occur spontaneously, during certain tissue infections, with use of indwelling GU or IV catheters, or after dental, GI, GU, wound-care, or other procedures. Bacteremia may cause metastatic infections, including endocarditis, especially in patients with valvular heart abnormalities. Transient bacteremia is often asymptomatic but may cause fever. Development of other symptoms usually suggests more serious infection, such as sepsis or septic shock (see p.).

Bacteremia may be transient and cause no sequelae, or it may have metastatic or systemic consequences. Systemic consequences include systemic inflammatory response syndrome and septic shock.

Etiology

Bacteremia has many possible causes, including

• Catheterization of an infected lower urinary tract

• Surgical treatment of an abscess or infected wound

• Colonization of indwelling devices, especially IV and intracardiac catheters, urethral catheters, and ostomy devices and tubes

Gram-negative bacteremia secondary to infection usually originates in the GU or GI tract or in the skin of patients with decubitus ulcers. Chronically ill and immunocompromised patients have an increased risk of gram-negative bacteremia. They may also develop bacteremia with gram-positive cocci, anaerobes, and fungi. Staphylococcal bacteremia is common among injection drug users and patients with IV catheters. *Bacteroides* bacteremia may develop in patients with infections of the abdomen and the pelvis, particularly the female genital tract. If an infection in the abdomen causes bacteremia, the organism is most likely a gram-negative bacillus. If an infection above the diaphragm causes bacteremia, the organism is most likely gram-positive.

Pathophysiology

Transient or sustained bacteremia can cause metastatic infection of the meninges or serous cavities, such as the pericardium or larger joints. Metastatic abscesses may occur almost anywhere. Multiple abscess formation is especially common with staphylococcal bacteremia. Bacteremia may cause endocarditis (see p.), most commonly with enterococcal, streptococcal, or staphylococcal bacteremia and less commonly with gram-negative bacteremia or fungemia. Patients with structural heart disease (eg, valvular disease, certain congenital anomalies), prosthetic heart valves, or other intravascular prostheses are predisposed to endocarditis. Staphylococci can cause bacterial endocarditis, particularly in injection drug users, and may involve the tricuspid valve.

Symptoms and Signs

Some patients are asymptomatic or have only mild fever. Development of symptoms such as tachypnea,

shaking chills, persistent fever, altered sensorium, hypotension, and GI symptoms (abdominal pain, nausea, vomiting, diarrhea) suggests sepsis or septic shock. Septic shock develops in 25 to 40% of patients with significant bacteremia.

Diagnosis

If bacteremia, sepsis, or septic shock is suspected, cultures are obtained of blood and any other appropriate specimens (see p.).

Treatment

• Antibiotics

In patients with suspected bacteremia, empiric antibiotics are given after appropriate cultures are obtained. Early treatment of bacteremia with an appropriate antimicrobial regimen appears to improve survival. Continuing therapy involves adjusting antibiotics according to the results of culture and susceptibility testing, surgically draining any abscesses, and usually removing any internal devices that are the suspected source of bacteria.

Biological Warfare and Terrorism

Biological warfare is the use of microbiological agents for hostile purposes. Such use is contrary to international law and has rarely taken place during formal warfare in modern history, despite the extensive preparations and stockpiling of biological agents carried out during the 20th century by most major powers. For a variety of reasons (including uncertain military efficacy and the threat of massive retaliation), experts consider the use of biological agents in formal warfare unlikely. The area of most concern is the use of such agents by terrorist groups. Biological agents are thought by some people to be an ideal weapon for terrorists. These agents may be delivered clandestinely, and they have delayed effects, allowing the user to remain undetected.

Potential biological agents include anthrax, botulinum toxin, brucellosis, encephalitis, viruses, hemorrhagic fever viruses (Ebola and Marburg), plague, tularemia, and smallpox. Each of these agents is potentially fatal and, except for anthrax and botulinum toxin, can be passed from person to person. Anthrax is of most concern; anthrax spores are relatively easy to prepare and spread through the air, creating the potential for distribution by airplane. Theoretically, 1 kg of anthrax could kill 10,000 people, although technical difficulties with preparing the spores in a sufficiently fine powder would probably limit actual deaths to a fraction of this number. Some other potential agents, including *Yersinia pestis*, *Francisella tularensis*, viral hemorrhagic fever viruses, smallpox virus, and botulinum toxin, can potentially be aerosolized as bioweapons.

Despite these theoretical concerns, the only successful terrorist use of anthrax—multiple pieces of contaminated mail delivered to a variety of locations in the US in 2001—resulted in only a handful of deaths and serious infections (total of 22 cases). A larger number of people were contaminated with anthrax spores without developing illness. However, there was extreme public anxiety related to these incidents, which may have been a major goal of the terror group responsible.

In addition to the actual infections, an even greater number of false threats of anthrax have been reported. In 1999, the FBI received an average of 1 false report/day of alleged anthrax use. False reports, both hoaxes and alarmed citizens misperceiving harmless material for anthrax, increased even more after the 2001 anthrax attack in the US.

The only other successful use of a biological agent by a terror group in the US occurred in 1984. In this event, 751 people were stricken with diarrhea when a salad bar in Oregon was intentionally contaminated with *Salmonella*. The bacteria were introduced by a religious cult trying to influence the results of a local election. No one died, and the election was not affected.

Defense against bioterrorism involves several factors:

 • Intelligence to disrupt terrorists before they can use the weapons

 • Early detection

 • Availability of protective antibiotics

 • Preparedness of public health infrastructure to coordinate management of an infectious disease outbreak

 • Vaccination of selected populations (eg, the military)

Chapter 130. Laboratory Diagnosis of Infectious Disease

Introduction

Laboratory tests may identify organisms directly (eg, visually, using a microscope, growing the organism in culture) or indirectly (eg, identifying antibodies to the organism). General types of tests include microscopy, culture, immunologic tests (agglutination tests such as latex agglutination, enzyme immunoassays, Western blot, precipitation tests, and complement fixation tests), and nucleic and non-nucleic acid-based identification methods. Culture is normally the gold standard for identification of organisms, but results may not be available for days or weeks, and not all pathogens can be cultured, making alternative tests useful. When a pathogen is cultured and identified, the laboratory can also assess its susceptibility to antimicrobial drugs.

Some tests (eg, Gram stain, routine aerobic culture) can detect a large variety of pathogens and are commonly done for many suspected infectious illnesses. However, because some pathogens are missed on these tests, clinicians must be aware of the limitations of each test for each suspected pathogen. In such cases, clinicians should request tests specific for the suspected pathogen (eg, special stains or culture media) or advise the laboratory to select more specific tests.

Microscopy

Microscopy can be done quickly, but accuracy depends on the experience of the microscopist and quality of equipment. Regulations often limit physicians' use of microscopy for diagnostic purposes outside a certified laboratory.

Most specimens are treated with stains that color pathogens, causing them to stand out from the background, although wet mounts of unstained samples can be used to detect fungi, parasites (including helminth eggs and larvae), vaginal clue cells, motile organisms (eg, *Trichomonas*), and syphilis (via darkfield microscopy). Visibility of fungi can be increased by applying 10% potassium hydroxide (KOH) to dissolve surrounding tissues and nonfungal organisms.

The clinician orders a stain based on the likely pathogens, but no stain is 100% specific. Most samples are treated with Gram stain and, if mycobacteria are suspected, with an acidfast stain. However, some pathogens are not easily visible using these stains; if these pathogens are suspected, different stains or other identification methods are required. Because microscopic detection usually requires a microbe concentration of about 1×10^5/mL, most body fluid specimens (eg, CSF) are concentrated (eg, by centrifugation) before examination.

Gram stain: The Gram stain classifies bacteria according to whether they retain crystal violet stain (gram-positive—blue) or not (gram-negative—red) and highlights cell morphology (eg, bacilli, cocci) and cell arrangement (eg, clumps, chains, diploids). Such characteristics can direct antibiotic therapy pending definitive identification. To do a Gram stain, technicians heat-fix specimen material to a slide and stain it by sequential exposure to Gram's crystal violet, iodine, decolorizer, and counterstain (typically safranin).

Acid-fast and moderate (modified) acid-fast stains: These stains are used to identify acid-fast organisms (*Mycobacterium* sp) and moderately acid-fast organisms (primarily *Nocardia* sp). These stains are also useful for staining *Rhodococcus* and related genera, as well as oocysts of some parasites (eg, *Cryptosporidium*).

Although detection of mycobacteria in sputum requires only about 5,000 to 10,000 organisms/mL, mycobacteria are often present in lower levels, so sensitivity is limited. Usually, several mL of sputum are decontaminated with Na hydroxide and concentrated by centrifugation for acid-fast staining. Specificity is better, although some moderately acid-fast organisms are difficult to distinguish from mycobacteria.

Fluorescent stains: These stains allow detection at lower concentrations (1×10^4 cells/mL). Examples are acridine orange (bacteria and fungi), auramine-rhodamine and auramine O (mycobacteria), and calcofluor white (fungi, especially dermatophytes).

Coupling a fluorescent dye to an antibody directed at a pathogen (direct or indirect immunofluorescence) should theoretically increase sensitivity and specificity. However, these tests are difficult to read and interpret, and few (eg, *Pneumocystis* and *Legionella* direct fluorescent antibody tests) are commercially available and commonly used.

India ink (colloidal carbon) stain: This stain is used to detect mainly *Cryptococcus neoformans* and other encapsulated fungi in a cell suspension (eg, CSF sediment). The background field, rather than the organism itself, is stained, making any capsule around the organism visible as a halo. In CSF, the test is not as sensitive as cryptococcal antigen. Specificity is also limited; leukocytes may appear encapsulated.

Wright's stain and Giemsa stain: These stains are used for detection of parasites in blood, *Histoplasma capsulatum* in phagocytes and tissue cells, intracellular inclusions formed by viruses and chlamydia, trophozoites of *Pneumocystis jirovecii*, and some intracellular bacteria.

Trichrome stain (Gomori-Wheatley stain) and iron hematoxylin stain: These stains are used to detect intestinal protozoa.

The Gomori-Wheatley stain is used to detect microsporidia. It may miss helminth eggs and larvae and does not reliably identify *Cryptosporidium*. Fungi and human cells take up the stain.

The iron hematoxylin stain differentially stains cells, cell inclusions, and nuclei. Helminth eggs may stain too dark to permit identification.

Culture

Culture is microbial growth on or in a nutritional solid or liquid medium; increased numbers of organisms simplify identification. Culture also facilitates testing of antimicrobial susceptibility.

Communication with the laboratory is essential. Although most specimens are placed on general purpose media (eg, blood or chocolate agar), some pathogens require inclusion of specific nutrients and inhibitors or other special conditions (see
Table 130-1); if one of these pathogens is suspected or if the patient has been taking antimicrobials, the laboratory should be advised. The specimen's source is reported so that the laboratory can differentiate pathogens from site-specific normal flora.

Specimen collection is important. The wrong type of swab can produce false-negative results. Wooden-shafted swabs are toxic to some viruses. Cotton-tipped swabs are toxic for some bacteria and chlamydiae. Blood cultures require decontamination and disinfection of the skin (eg, povidone iodine swab, allowed to dry, removed with 70% alcohol). Multiple samples, each from a different site are generally used; they are taken nearly simultaneously with fever spikes if possible. Normal flora of skin and mucous membranes that grows in only a single blood sample is usually interpreted as contamination. If a blood specimen is obtained from a central line, a peripheral blood specimen should also be obtained to help differentiate systemic bacteremia from catheter infection. Cultures from infected catheters generally turn positive more quickly and contain more organisms than simultaneously drawn peripheral blood cultures. Some fungi, particularly molds (eg, *Aspergillus* sp), usually cannot be cultured from blood.

[**Table 130-1.** Selective Media for Isolation of Common Bacteria]

The specimen must be transported rapidly, in the correct medium, and in conditions that limit growth of any potentially contaminating normal flora. For accurate quantification of the pathogen, additional pathogen growth must be prevented; specimens should be transported to the laboratory immediately or, if transport is delayed, refrigerated (in most cases).

Certain cultures have special considerations.

Anaerobic bacteria should not be cultured from sites where they are normal flora because differentiation of pathogens from normal flora may be impossible. Specimens must be shielded from air, which can be

difficult. For swab specimens, anaerobic transport media are available. Specimens collected with a syringe (eg, abscess contents) should be transported in the syringe.

Mycobacteria are difficult to culture. Specimens containing normal flora (eg, sputum) must first be decontaminated and concentrated. *Mycobacterium tuberculosis* and some other mycobacteria grow slowly. Growth of *M. tuberculosis* is typically faster in liquid than in solid media; routine use of automated systems with liquid media can result in growth within 2 wk vs ≥ 4 wk on solid media such as Lowenstein-Jensen agar. In addition, few organisms may be present in a specimen. Multiple specimens from the same site may help maximize yield. Specimens should be allowed to grow for 8 wk before being discarded. If an atypical mycobacterium is suspected, the laboratory should be notified.

Viruses are generally cultured from swabs and tissue specimens usually transported in media that contain antibacterial and antifungal agents. Specimens are inoculated onto tissue cultures that support the suspected virus and inhibit all other microbes. Viruses that are highly labile (eg, varicella zoster) should be inoculated onto tissue cultures within 1 h of collection. Standard tissue cultures are most sensitive. Rapid tissue cultures (shell vials) may provide more rapid results. Some common viruses cannot be detected using routine culture methods and require alternative methods for diagnosis (eg, enzyme immunoassay for Epstein-Barr virus, hepatitis B and E viruses, HIV, and human T-lymphotropic virus; serologic tests for hepatitis A and D viruses; nucleic acid-based methods for HIV).

Fungi specimens obtained from nonsterile sites must be inoculated onto media containing antibacterial agents. Specimens should be allowed to grow for 4 wk before being discarded.

Susceptibility Testing

Susceptibility tests determine a microbe's vulnerability to antimicrobial drugs by exposing a standardized concentration of organism to specific concentrations of antimicrobial drugs. Susceptibility testing can be done for bacteria, fungi, and viruses. For some organisms, results obtained with one drug predict results with similar drugs. Thus, not all potentially useful drugs are tested.

Susceptibility testing occurs in vitro and may not account for many in vivo factors (eg, pharmacodynamics and pharmacokinetics, site-specific drug concentrations, host immune status, site-specific host defenses) that influence treatment success. Thus, susceptibility test results do not always predict treatment outcome.

Susceptibility testing can be done qualitatively, semiquantitatively, or using nucleic acid-based methods. Testing can also determine the effect of combining different antimicrobials (synergy testing).

Qualitative methods: Qualitative methods are less precise than semiquantitative. Results are usually reported as susceptible (S), intermediate (I), or resistant (R). The commonly used disk diffusion method (also known as the Kirby-Bauer test) is appropriate for rapidly growing organisms. It places antibiotic-impregnated disks on agar plates inoculated with the test organism. After incubation (typically 16 to 18 h), the diameter of the zone of inhibition around each disk is measured. Each organism-antibiotic combination has different diameters signifying S, I, or R.

Other methods that require less rigid adherence to test parameters can be used to rapidly screen for resistance of a single organism to a single drug or drug class or to specific antimicrobial combinations (eg, oxacillin resistance of methicillin-resistant *Staphylococcus aureus*, β-lactamase production).

Semiquantitative methods: Semiquantitative methods determine the minimal concentration of a drug that inhibits growth of a particular organism in vitro. This minimum inhibitory concentration (MIC) is reported as a numerical value that may then be translated to 1 of 3 groupings: S (sensitive), I (intermediate), or R (resistant). MIC determination is used primarily for bacteria, including mycobacteria and anaerobes, and is sometimes used for fungi, especially *Candida* sp, obtained from sterile sites. Minimal killing (bactericidal) concentration (MBC) can also be determined but is technically difficult, and standards for interpretation have not been agreed on. The value of MBC testing is that it indicates whether a drug may be bacteriostatic or bactericidal.

The antibiotic can be diluted in agar or broth, which is then inoculated with the organism. Broth dilution is the gold standard but is labor intensive because only one drug concentration can be tested per tube. A more efficient method uses a strip of polyester film impregnated with antibiotic in a concentration gradient along its length. The strip is laid on an agar plate containing the inoculum, and the MIC determined by the location on the strip where inhibition begins; multiple antibiotics can be tested on one plate.

The MIC allows correlation between drug susceptibility of the organism and the achievable tissue concentration of drug not bound to protein (free drug). If the tissue concentration of free drug is higher than the MIC, successful treatment is likely. Similarly, reports of S, I, and R are correlated with MIC but generally are not tissue concentration-specific. That is, they are usually based on achievable serum or plasma concentration of free drug.

Nucleic acid-based methods: These tests incorporate nucleic acid techniques similar to those used for organism identification (see p. 1170) but modified to detect known resistance genes or mutations. An example is mecA, a gene for oxacillin resistance in *S. aureus*; if this gene is present, the organism is considered resistant to all β-lactam drugs regardless of apparent susceptibility results. However, although a number of such genes are known, their presence does not uniformly confer in vivo resistance. Also, because new mutations or other resistance genes may be present, their absence does not guarantee drug sensitivity. For these reasons and because the tests are limited in number, expensive, and not widely available, nucleic acid methods have not replaced standard culture and routine susceptibility testing.

Immunologic Tests

Immunologic tests use an antigen to detect antibodies to a pathogen or use an antibody to detect an antigen of the pathogen in the patient's specimen. Handling varies, but if testing is to be delayed, the specimen should typically be refrigerated or frozen to prevent overgrowth of bacterial contaminants.

Agglutination tests: In agglutination tests (eg, latex agglutination, coaggregation), a particle (latex bead or bacterium) is coupled to a reagent antigen or antibody. The resulting particle complex is mixed with the specimen (eg, CSF, serum); if the target antibody or antigen is present in the specimen, it cross-links the particles, producing measurable agglutination.

If results are positive, the body fluid is serially diluted and tested. Agglutination with more dilute solutions indicates higher concentrations of the target antigen or antibody. The titer is correctly reported as the reciprocal of the most dilute solution yielding agglutination; eg, 32 indicates that agglutination occurred in a solution diluted to 1/32 of the starting concentration.

Usually, agglutination tests are rapid but less sensitive than many other methods. They can also determine serotypes of some bacteria.

Complement fixation: This test measures complement-consuming (complement-fixing) antibody in serum or CSF. The test is used for diagnosis of some viral and fungal infections, particularly coccidioidomycosis. The specimen is incubated with known quantities of complement and the antigen that is the target of the antibody being measured. The degree of complement fixation indicates the relative quantity of the antibody in the specimen. The test can measure IgM and IgG antibody titers or can be modified to detect certain antigens. It is accurate but has limited applications, is labor intensive, and requires numerous controls.

Enzyme immunoassays: These tests use antibodies linked to enzymes to detect antigens and to detect and quantify antibodies. The enzyme immunoassay (EIA) and enzyme-linked immunosorbent assay (ELISA) are examples. Because sensitivities of most enzyme immunoassays are high, they are usually used for screening. Titers can be determined by serially diluting the specimen as for agglutination tests.

Test sensitivities, although usually high, can vary, sometimes according to patient age, microbial serotype, specimen type, or stage of clinical disease.

Precipitation tests: These tests measure an antigen or antibody in body fluids by the degree of visible precipitation of antigen-antibody complexes within a gel (agarose) or in solution. There are many types of

precipitation tests (eg, Ouchterlony double diffusion, counter immunoelectrophoresis), but their applications are limited. Usually, a blood specimen is mixed with test antigen to detect patient antibodies, most often in suspected fungal infection or pyogenic meningitis. Because a positive result requires a large amount of antibody or antigen, sensitivity is low.

Western blot test: This test detects antimicrobial antibodies in the patient's sample (eg, serum, other body fluid) by their reaction with target antigens (eg, viral components) that have been immobilized onto a membrane by blotting.

The Western blot typically has good sensitivity, although often less than that of screening tests such as ELISA, but generally is highly specific. Thus, it is usually used to confirm a positive result obtained with a screening test.

Technical modifications of the Western blot are the line immunoassay (LIA); the recombinant immunoblot assay (RIBA), which uses synthetic or recombinant-produced antigens; and immunochromatographic assays, which can rapidly screen specimens for specific microbial antigens or patient antibodies.

Non-Nucleic Acid-Based Identification Methods

Once an organism has been isolated by culture, it must be identified. Non-nucleic acid-based identification methods use phenotypic (functional or morphologic) characteristics of organisms rather than genetic identification.

Characteristics of an organism's growth on culture media, such as colony size, color, and shape, provide clues to species identification and, combined with Gram stain, direct further testing. Numerous biochemical tests are available; each is restricted to organisms of a certain type (eg, aerobic or anaerobic bacteria). Some assess an organism's ability to use different substrates for growth. Others assess presence or activity of key enzymes (eg, coagulase, catalase). Tests are done sequentially, with previous results determining the next test to be used. The sequences of tests are myriad and differ somewhat among laboratories.

Non-nucleic acid-based identification tests may involve manual methods, automated systems, or chromatographic methods. Some commercially available kits contain a battery of individual tests that may be done simultaneously using a single specimen and may be useful for a wider range of organisms. Multiple test systems can be highly accurate but may require several days to yield results.

Chromatographic methods: Microbial components or products are separated and identified using high-performance liquid chromatography (HPLC) or gas chromatography. Usually, identification is by comparison of an organism's fatty acids to a database. Chromatographic methods can be used to identify aerobic and anaerobic bacteria, mycobacteria, and fungi. Test accuracy depends on the conditions used to culture the specimen and the quality of the database, which may be inaccurate or incomplete.

Nucleic Acid-Based Identification Methods

Nucleic acid-based methods detect organism-specific DNA or RNA sequences extracted from the microorganism. Sequences may or may not be amplified in vitro. Nucleic acid-based methods are generally specific and highly sensitive and can be used for all categories of microbes. Results can be provided rapidly. Because each test typically is specific to a single organism, the clinician must know the diagnostic possibilities and request tests accordingly. For example, if a patient has symptoms suggesting influenza but the influenza season is over, doing a more general viral diagnostic test (eg, viral culture) rather than a specific flu test is better because another virus (eg, parainfluenza, adenovirus) may be the cause.

Nucleic acid-based tests are qualitative, but quantification methods exist for a limited but increasing number of infections (eg, HIV, cytomegalovirus, human T-cell lymphotropic virus); these methods can be useful for diagnosis and for monitoring response to treatment.

Techniques that do not involve nucleic acid amplification are used if the organism has been first cultured

or is present in high concentration in the specimen (eg, in pharyngitis caused by group A *Streptococcus*, in genital infections caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*).

Amplification: Nucleic acid amplification techniques take tiny amounts of DNA or RNA, replicate them many times, and thus can detect minute traces of an organism in a specimen, avoiding the need for culture. These techniques are particularly useful for organisms that are difficult to culture or identify using other methods (eg, viruses, obligate intracellular pathogens, fungi, mycobacteria, some other bacteria) or that are present in low numbers.

These tests may involve target amplification (eg, PCR, reverse transcriptase-PCR [RT-PCR], strand displacement amplification, transcription amplification), signal amplification (eg, branched DNA assays, hybrid capture), probe amplification (eg, ligase chain reaction, cleavase-invader, cycling probes), or postamplification analysis (eg, sequencing of the amplified product, microarray analysis, and melting curve analysis, as is done in real-time PCR).

Appropriate specimen collection and storage before arrival at the molecular diagnostic laboratory are critical. Because amplification methods are so sensitive, false positives from trace contamination of the specimen or equipment can easily occur. Despite high sensitivity, false negatives sometimes occur even when a patient is symptomatic (eg, in West Nile virus infection). False-negative results can be minimized by

• Avoiding use of swabs with wooden shafts or cotton tips

• Transporting specimens rapidly

• Freezing or refrigerating specimens if transport is likely to take > 2 h

Freezing is the typical storage method for nucleic acid amplification assays. However, specimens should be refrigerated rather than frozen if labile viruses (eg, varicella-zoster virus, influenza virus, HIV-2) are suspected or if viral cultures are also to be done (frozen specimens may not be usable for standard cultures).

Chapter 131. Immunization

Introduction

Immunity can be achieved actively by using antigens (eg, vaccines, toxoids) or passively by using antibodies (eg, immune globulins, antitoxins). A toxoid is a bacterial toxin that has been modified to be nontoxic but that can still stimulate antibody formation. A vaccine is a suspension of whole (live or inactivated) or fractionated bacteria or viruses rendered nonpathogenic. For vaccines available in the US, see

Table 131-1. The most current recommendations for immunization are available at the Centers for Disease Control and Prevention (CDC) web site.

Vaccines should be given exactly as recommended on the package insert; however, the interval between a series of doses may be lengthened without losing efficacy. Injection vaccines are usually given IM into the mid-lateral thigh (in infants and toddlers) or into the deltoid muscle (in school-aged children and adults). Parents should keep a written history of each child's vaccinations.

[**Table 131-1.** Vaccines Available in the US]

Risks, Restrictions, and High-Risk Groups

Live-microbial vaccines should not be given simultaneously with blood, plasma, or immune globulin, which can interfere with development of desired antibodies; ideally, such vaccines should be given 2 wk before or 6 to 12 wk after the immune globulins.

Immunocompromised patients should not receive live-virus vaccines, which could provoke severe or fatal infections. In patients receiving short-term (ie, < 14 days) immunosuppressive therapy (eg, corticosteroids, antimetabolites, alkylating compounds, radiation), live-virus vaccines should be withheld until after treatment. Patients receiving longer-term immunosuppressive therapy may receive inactivated vaccines such as DTaP; ≥ 3 mo after immunosuppressive therapy is stopped, they should be given an additional dose of inactivated vaccine and may receive live-virus vaccines.

Asplenic patients are predisposed to overwhelming bacteremic infection, usually due to *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type b (Hib). They should be given the following:

• Hib conjugate vaccine (HbCV)

• Meningococcal polysaccharide vaccine

• Annual influenza vaccine

• Pneumococcal conjugate (if age < 5 yr) or polysaccharide (if age > 5 yr) vaccine

Before solid organ transplantation, patients should receive all appropriate vaccines. Patients who have had hematopoietic cell transplantation should be considered unimmunized and should receive repeat doses of all appropriate vaccines.

Patients with AIDS should generally receive inactivated vaccines (eg, DTP, polio [IPV], HbCV) according to routine recommendations but should usually not receive live-virus or bacterial vaccines (eg, measles-mumps-rubella, OPV, BCG). However, they can receive measles-mumps-rubella if immunosuppression is not severe because naturally occurring measles can cause severe, often fatal infection in AIDS patients, and measles-mumps-rubella vaccine rarely causes serious complications.

Risks of vaccines should be discussed with patients. Parents should give written consent for vaccination of their children. In the US, selected events that occur after routine vaccination must be reported to the manufacturer, the US Department of Health and Human Services, and the Centers for Disease Control

and Prevention's Vaccine Adverse Event Reporting System (VAERS). Forms and instructions can be obtained by calling 800-822-7967 (Health and Human Services) or from the VAERS web site (http://vaers.hhs.gov).

A temperature of > 39° C requires delaying vaccination, but minor infections, such as the common cold (even with low-grade fever), do not. Some vaccines produced in cell culture systems contain trace amounts of egg antigens. Although egg allergies are often considered contraindications to these vaccines, the vaccines do not appear to cause significant adverse reactions in patients who can eat foods that contain eggs, such as bread or cookies. A history of other allergic reactions may contraindicate use of certain vaccines (see
Table 131-2).

Pregnancy is a relative contraindication to vaccination with human papillomavirus (HPV), measles-mumps-rubella, pneumococcal pneumonia, varicella, and other live-virus vaccines.

Concern has been raised about the safety in infants of thimerosal, an Hg-based preservative present in some vaccines, but there is no evidence of harm. In particular, there is no convincing evidence that vaccines containing thimerosal are related to the development of autism. Nevertheless, most manufacturers have developed thimerosal-free vaccines for use in infants. Information about vaccines that currently contain low levels of Hg or thimerosal is available at the Institute for Vaccine Safety web site.

Patients with a fluctuating or progressive neurologic disorder, such as Guillain-Barre syndrome, should not be vaccinated until their condition has been stable for at least 1 yr because cerebral irritation is a risk. If a neurologic disorder is stable, vaccinations should proceed normally. The risk in patients with multiple sclerosis is unknown.

Routine Vaccinations

For the schedule of vaccinations for infants and children, see
Table 268-10 on p. 2718 (see also the Centers for Disease Control and Prevention's [CDC's] National Immunization Program 2010 Childhood and Adolescent Immunization Schedule at www.cdc.gov/vaccines/recs/schedules/).

For vaccinations to be considered for all adults, see Table 131-2 (see also the CDC's National Immunization Program Adult Immunization Recommendations at www.cdc.gov/vaccines/recs/schedules/adult-schedule). Uses of nonroutine active vaccines (eg, for rabies, typhoid, yellow fever, and mycobacterial infections) and some routine vaccinations are discussed under specific disorders elsewhere in THE MANUAL.

Diphtheria-Tetanus-Pertussis

Preparations: Diphtheria (D) vaccines contain toxoids prepared from *Corynebacterium diphtheriae*. Tetanus (T) vaccines contain toxoids prepared from *Clostridium tetani*. Acellular (a) pertussis (P) vaccines contain semipurified or purified components of *Bordetella pertussis*. Whole-cell pertussis vaccine is no longer available in the US because of concerns about adverse effects, but it is still available in other parts of the world. There are 2 preparations of the acellular vaccine:

• DTaP for children < 7 yr

• Tdap for adolescents and adults

Tdap contains lower doses of diphtheria and pertussis components (indicated by the lower case d and p).

Administration: The vaccine is given as 5 primary and 1 booster IM injections during childhood as follows: the first 3 doses at 2-mo intervals, starting at age 2 mo; the 4th at age 12 to 15 mo; and the last before school entry at age 4 to 6 yr. A single booster of Tdap is given at age 11 or 12 yr.

Adverse effects: Adverse effects are rare and are mostly attributable to the pertussis component. They include encephalopathy within 7 days; a seizure, with or without fever, within 3 days; persistent, severe, inconsolable screaming or crying for ≥ 3 h; collapse or shock within 48 h; temperature of ≥ 40.5° C, unexplained by another cause, within 48 h; and immediate severe or anaphylactic reaction to the vaccine. These reactions contraindicate further use of pertussis vaccine; combined diphtheria and tetanus vaccine is available without the pertussis component.

Mild adverse effects include redness, swelling, and soreness at the injection site.

Tetanus-Diphtheria

Although tetanus is rare in the US, it has a high mortality rate. Because one third of cases

[**Table 131-2.** Common Vaccinations for Adults]

occur unpredictably (after minor or inapparent injuries), universal tetanus vaccination remains necessary.

Preparations: The most widely used preparations combine tetanus toxoid with diphtheria toxoid (Td for adults, DT for children); a preparation with only tetanus toxoid (TT) is also available. Td contains a lower dose of diphtheria toxoid than DTaP and DT, which are used in children.

Administration: Td boosters, 0.5 mL IM, are given every 10 yr after the Tdap booster that is given at age 11 to 12 yr. Boosters are needed to maintain immunity. Because the incidence of pertussis is increasing, at least one booster before age 65 should be Tdap. Adults who missed the primary series of vaccinations in childhood should receive it as adults.

Adverse effects: Adverse effects are very rare. They include anaphylactic reactions, Guillain-Barre syndrome, and brachial neuritis. Mild effects include redness, swelling, and soreness at the injection site.

Haemophilus influenzae Type b

Preparations: These vaccines are prepared from the purified capsule of *Haemophilus influenzae* type b (Hib). All Hib vaccines use polyribosylribitol phosphate (PRP) as the polysaccharide, but 4 different protein carriers produce 4 different Hib conjugate vaccines: diphtheria toxoid (PRP-D), *Neisseria meningitidis* outer membrane protein (PRP-OMP), tetanus toxoid (PRP-T), and diphtheria mutant carrier protein CRM_{197} (HbOC).

Administration: A primary series is given in 3 IM doses at age 2, 4, and 6 mo or in 2 IM doses at age 2 and 4 mo, depending on the formulation. In either case, a booster is recommended at age 12 to 15 mo. Some adults at increased risk (eg, because of AIDS or asplenia) may benefit from this vaccine.

Adverse effects: Adverse effects are rare. They can include pain, redness, and swelling at the injection site.

Hepatitis A

Preparations: Hepatitis A vaccines are prepared from formalin-inactivated, cell culture-derived hepatitis A virus. There are 2 formulations; either can be used in children or adults.

Administration: The vaccine is given in 2 IM doses 6 mo apart. It is recommended for children aged 12 to 18 mo and for older children and adults who are at increased of the disease (see Table 131-2).

Adverse effects: No serious adverse effects have been reported. Mild effects include pain and occasionally induration at the injection site.

Hepatitis B

Preparations: Hepatitis B vaccine uses recombinant DNA technology. Single-antigen and combination

formulations are available.

Administration: The vaccine is given in 2 or 3 IM doses, depending on the formulation. Universal vaccination is recommended beginning at birth.

Adverse effects: Serious adverse effects are very rare and include anaphylaxis. Mild effects include pain at the injection site and occasionally an increase in temperature to > 38°C.

Human Papillomavirus

Preparations: Recombinant technology is used to prepare the vaccine. The vaccine is made from HPV-like particles (VLP) from serotypes 6, 11, 16, and 18, which cause 70% of cervical cancers and 90% of genital warts.

Administration: The vaccine is given in 3 IM doses: initially, then at 1 to 2 and 4 to 6 mo after the initial dose. It is recommended for females aged 11 to 13 but can be given as early as age 9 or up to age 26 for catch-up. Vaccination is not recommended after age 26.

Adverse effects: No serious adverse effects have been reported. Mild effects include redness, swelling, and tenderness at the injection site.

Influenza

Preparations: Influenza vaccines may be inactivated trivalent vaccines (TIV) or live-attenuated vaccines (LAIV). Each type targets 3 virus strains (2 from influenza A and 1 from influenza B). Because antigenic drift is continual, 1 or 2 strains are changed each year in anticipation of the expected predominant influenza strains. An inactivated vaccine against avian influenza has been developed but is not commercially available. It is being nationally stockpiled in case person-to-person transmission of avian influenza becomes possible.

Administration: The vaccine is required annually for at-risk patients because of antigenic drift. Because outbreaks usually begin in early winter or midwinter, the vaccine is given in the fall, usually October and November in the Northern Hemisphere.

TIV, given as a single IM injection, is recommended for people at high risk of serious sequelae, including children aged 6 mo to 8 yr and anyone > 50 yr (see Table 131-2), as well as anyone who requests vaccination.

LAIV, given as an intranasal spray, is indicated for healthy people aged 2 to 49 yr; it is contraindicated during pregnancy.

Adverse effects: Rarely, TIV has adverse effects, such as Guillain-Barre syndrome, anaphylactic reactions, soreness at the injection site, and fever. Adverse effects of LAIV are unusual; they include possible triggering of asthma and transmission of the virus to unimmunized contacts.

Egg protein is used in both vaccine types; thus, the vaccine is contraindicated for people who have severe anaphylactic reactions to egg protein.

Measles, Mumps, and Rubella

Preparations: The vaccine contains live-attenuated virus prepared in chicken embryo cell cultures. Measles vaccine is available as a single-antigen (measles-only) vaccine or combined with rubella (MR), mumps and rubella (MMR), or mumps, rubella, and varicella (MMRV). There are also single-antigen vaccines for mumps, rubella, and varicella.

Administration: Most commonly, the combination vaccine MMR or MMRV is given sc. The vaccine should be given to all children in their 2nd yr of life, typically at age 12 to 15 mo, with a 2nd dose at age 4 to 6 yr. Adults at risk include those who have never received the vaccine and have never become

naturally infected. Generally, people born before 1956 are considered immune because infection during their childhood was ubiquitous. Unless the vaccine is contraindicated, people who were born after 1956 and have not had 2 doses of the vaccine or the infections should receive at least one dose of the combined vaccine; people who have been or are likely to be exposed (eg, college students, health care workers, international travelers) should receive a 2nd dose.

Although the components of the vaccine can be given separately, the combined form is preferred because people who need one vaccine probably need all 3, and revaccination poses no particular risk.

Adverse effects: A mild, noncommunicable infection occurs in 15% of vaccine recipients. Symptoms appear 7 to 11 days after immunization and include fever, malaise, and a measles-like exanthem. Mumps vaccine has adverse effects only rarely; they include encephalitis (only from a Japanese mumps vaccine strain), seizures, nerve deafness, parotitis, purpura, rash, and pruritus.

Rubella vaccine can cause joint pain, usually in the small peripheral joints 2 to 8 wk after immunization, in < 1% of infants but in ≤ 26% of women. Rash or lymphadenopathy occasionally occurs. The vaccine is not recommended for pregnant women because of the theoretic risk to the fetus. However, inadvertent administration during pregnancy does not necessarily mean a therapeutic abortion is recommended because the actual fetal risk may be nil.

With all of the vaccine formulations, local adverse effects are unusual and include soreness at the injection site.

Pneumococcal Disease

Preparations: Pneumococcal conjugate vaccine (PCV7) contains 7 purified capsular polysaccharides of *Streptococcus pneumoniae*; each is coupled to a variant of diphtheria toxin. Pneumococcal polysaccharide vaccine (PPV23) contains antigens from the 23 most virulent of the 83 subtypes of *S. pneumococcus*. Unlike the older 23-valent vaccine, PCV7 can stimulate antibody responses in infants. It also seems to confer greater protection against invasive pneumococcal disorders than PPV23. PPV23 reduces bacteremia by 56 to 81% in adults overall but is less effective in debilitated elderly people. It reduces pneumonia incidence only minimally.

Administration: PCV7 is recommended as a 4-dose IM series for infants at age 2, 4, 6, and 12 to 15 mo. Children at high risk of pneumococcal disease (eg, children with sickle cell disease, asplenia, or a chronic disorder) should receive a dose of PPV23 at age 24 mo and an additional dose 3 to 5 yr after the first. PPV23 should be given to any older child or adult at high risk of pneumococcal disease (see Table 131-2). One immunization is recommended for lifetime protection; however, revaccination after 5 yr should be considered for patients at particularly high risk.

Adverse effects: Adverse effects are usually mild and include fever, irritability, drowsiness, anorexia, vomiting, and local erythema.

Poliomyelitis

Preparations: Inactivated poliovirus vaccine (IPV) contains a mixture of formalininactivated poliovirus types 1, 2, and 3. IPV may contain trace amounts of streptomycin, neomycin, and polymyxin B. A combination vaccine with IPV, DTaP, and hepatitis B is also available. The live-attenuated oral formulation is no longer available in the US because it causes polio in about 1 of every 2.4 million people who receive the vaccine.

Administration: A 4-dose IM series is given at age 2 mo, 4 mo, 6 to 18 mo, and 4 to 6 yr. Typically, a combination vaccine is used for the first 3 vaccinations and a single-antigen vaccine for the last dose.

Adverse effects: No adverse effects have been associated with IPV. Because it may contain trace amounts of neomycin, streptomycin, and polymyxin B, people who are sensitive to any of these drugs may have an allergic reaction to the vaccine.

Varicella

Preparations: The vaccine contains an attenuated wild strain of varicella and trace amounts of gelatin and neomycin. It is available as a single-antigen vaccine or as a combination vaccine with MMR.

Administration: The vaccine is given sc in 2 doses: at age 12 to 15 mo and at age 4 to 6 yr. The 2nd dose is a new recommendation; thus, a catch-up dose is suggested for children, adolescents, and adults who have received only one dose. The vaccine should be given to all children and to young adults not previously infected, especially health care practitioners and close contacts of immunocompromised patients. If adults have not had varicella, levels of protective antibodies should be measured to determine the need for vaccination. No immune globulins, particularly varicella-zoster immune globulin, should be given within 5 mo before or 2 mo after vaccination because immune globulins may prevent development of protective antibodies.

Adverse effects: Adverse effects are minimal and include transient pain, tenderness, and redness at the injection site. Occasionally, within 1 mo of vaccination, a mild maculopapular or varicella-like rash develops. Patients who develop this rash should avoid contact with immunocompromised people until it resolves. Spread of the virus from vaccine recipients to susceptible people has been documented in < 1% of recipients but only from those who developed a rash.

Because Reye's syndrome can develop, recipients < 16 yr should avoid salicylates for 6 wk.

Herpes Zoster

Preparations: The vaccine contains an attenuated wild strain of varicella, similar to the varicella vaccine but with a higher amount of the attenuated virus.

Administration: The vaccine is recommended for adults ≥ 60 yr regardless of prior infection. It is given sc.

Adverse effects: No serious adverse effects have been reported. Soreness at the site of the injection may occur.

Simultaneous Administration of Different Vaccines

Simultaneous administration is safe, effective, and convenient; it is particularly recommended when children may be unavailable for future vaccination or when adults require multiple simultaneous vaccines (eg, before international travel). Simultaneous administration may involve combination vaccines (see Table 131-1) or use of ≥ 1 single-antigen vaccines. More than one vaccine may be given at the same time using different injection sites and syringes. If live-virus vaccines (varicella and MMR) are not given at the same time, they should be given at least 4 wk apart.

Immunizations for Travelers

Immunizations may be required for travel to areas where infectious diseases are endemic. The Centers for Disease Control and Prevention can provide information; a telephone service (1-877-394-8747) and web site (wwwnc.cdc.gov/travel/content/vaccinations.aspx) are available 24 h/day.

Passive Immunization

Passive immunization is provided in the following circumstances:

• When people cannot synthesize antibody

• When people have been exposed to a disease that they are not immune to or that is likely to cause complications

• When people have a disease and the effects of the toxin must be ameliorated

For immune globulins and antitoxins available in the US, see
Table 131-3.

Human immune globulin (IG): IG is a concentrated antibody-containing solution prepared from plasma obtained from normal donors. It consists primarily of IgG, although trace amounts of IgA, IgM, and other serum proteins may be present. IG very rarely contains transmissible viruses (eg, hepatitis B or C, HIV) and is stable for many months if stored at 4°C. IG is given IM. Because maximal serum antibody levels may not occur until about 48 h after IM injection, IG must be given as soon after exposure as possible. Half-life of IG in the circulation is about 3 wk.

IG may be used for prophylaxis in hepatitis A, measles, immunoglobulin deficiency, varicella (in immunocompromised patients when varicella-zoster IG is unavailable), and rubella exposure during the 1st trimester of pregnancy.

[**Table 131-3.** Immune Globulins and Antitoxins* Available in the US]

IG provides only temporary protection; the antibody content against specific agents varies by as much as 10-fold among preparations. Administration is painful, and anaphylaxis can occur.

IV immune globulin (IVIG) was developed to provide larger and repeated doses of human immune globulin. IVIG is used to treat or prevent severe bacterial and viral infections, autoimmune disorders, and immunodeficiency disorders, particularly the following:

• Kawasaki disease

• HIV infection in children

• Chronic B-cell lymphocytic leukemia

• Primary immunodeficiencies

• Autoimmune thrombocytopenic purpura

• Prevention of graft-vs-host disease

IVIG or a specific monoclonal antibody against RSV is available for prevention of RSV in children who are < 24 mo and have bronchopulmonary dysplasia or a history of premature birth (< 35 wk gestation).

Adverse effects are uncommon, although fever, chills, headache, faintness, nausea, vomiting, hypersensitivity, anaphylactic reactions, coughing, and volume overload have occurred.

Subcutaneous immune globulin (SCIG) is also prepared from pooled human plasma; SCIG is intended for home use in patients with a primary immunodeficiency.

Injection site reactions are common, but systemic adverse effects (eg, fever, chills) are much less common than with IVIG.

Hyperimmune globulin: Hyperimmune globulin is prepared from the plasma of people with high titers of antibody against a specific organism or antigen. It is derived from people convalescing from natural infections or donors artificially immunized.

Hyperimmune globulins are available for hepatitis B, respiratory syncytial virus (RSV), rabies, tetanus, cytomegalovirus, vaccinia, and varicella-zoster. Administration is painful, and anaphylaxis may occur.

Chapter 132. Bacteria and Antibacterial Drugs

Introduction

Bacteria are microorganisms that have circular double-stranded DNA and (except for mycoplasmas) cell walls. Most bacteria live extracellularly. Some bacteria (eg, *Salmonella typhi; Neisseria gonorrhoeae; Legionella, Mycobacterium, Chlamydia*, and *Chlamydophila* spp) preferentially reside and replicate intracellularly. Some bacteria such as chlamydiae and rickettsiae are obligate intracellular pathogens (ie, able to grow, reproduce, and cause disease only within the cells of the host). Others (eg, *Salmonella typhi, Brucella* sp, *Francisella tularensis, N. gonorrhoeae, N. meningitidis, Legionella* and *Listeria* spp, *Mycobacterium tuberculosis*) are facultative intracellular pathogens.

Many bacteria are present in humans as normal flora, often in large numbers and in many areas (eg, in the GI tract). Only a few bacterial species are human pathogens.

Bacteria are classified by the following criteria (see Table 132-1).

Morphology: Bacteria may be cylindric (bacilli), spherical (cocci), or spiral (spirochetes). A few coccal, many bacillary, and most spirochetal species are motile.

Staining: The most common stain for general bacterial identification is Gram stain. Gram-positive bacteria retain crystal violet dye (appearing dark blue) after iodine fixation and alcohol decolorization; gram-negative bacteria do not. Gram-negative bacteria have an additional outer membrane containing lipopolysaccharide (endotoxin), increasing the virulence of these bacteria. (For other factors that enhance bacterial pathogenicity, see Factors Facilitating Microbial Invasion on p. 1150.)

Ziehl-Neelsen stain (acid-fast stain) is used to identify mainly mycobacteria, particularly *M. tuberculosis*. It also can identify *Nocardia* sp. Carbolfuchsin is applied with heat, followed by decolorization with hydrochloric acid and ethanol and counterstaining with methylene blue.

Encapsulation: Some bacteria are enclosed in capsules; for some encapsulated bacteria (eg, *Streptococcus pneumoniae, Haemophilus influenzae*), the capsule helps protect them from ingestion by phagocytes. Encapsulation increases bacterial virulence.

Oxygen requirements: Aerobic bacteria (obligate aerobes) require O_2 to produce energy and to grow in culture. They produce energy using aerobic cellular respiration.

Anaerobic bacteria (obligate anaerobes) do not require O_2 and do not grow in culture if air is present. They produce energy using fermentation or anaerobic respiration. Anaerobic bacteria are common in the GI tract, vagina, dental crevices, and wounds when blood supply is impaired.

Facultative bacteria can grow with or without O_2. They produce energy by fermentation or anaerobic respiration when O_2 is absent and by aerobic cellular respiration when O_2 is present. Microaerophilic bacteria prefer a reduced O_2

[**Table 132-1.** Classification of Common Pathogenic Bacteria]

tension (eg, 2 to 10%). Chlamydiae are obligate intracellular parasites that acquire energy from the host cell and do not produce it themselves.

Antibacterial Drugs

Antibacterial drugs are derived from bacteria or molds or are synthesized de novo. Technically, "antibiotic" refers only to antimicrobials derived from bacteria or molds but is often (including in THE MANUAL) used synonymously with "antibacterial drug."

Antibiotics have many mechanisms of action, including inhibiting cell wall synthesis, activating enzymes that destroy the cell wall, increasing cell membrane permeability, and interfering with protein synthesis and nucleic acid metabolism.

Antibiotics sometimes interact with other drugs, raising or lowering serum levels of other drugs by increasing or decreasing their metabolism or by various other mechanisms (see Table 132-2). The most clinically important interactions involve drugs with a low therapeutic ratio (ie, toxic levels are close to therapeutic levels). Also, other drugs can increase or decrease levels of antibiotics.

Many antibiotics are chemically related and are thus grouped into classes. Although drugs within each class share structural and functional similarities, they often have different pharmacology and spectra of activity.

Selection and Use of Antibiotics

Antibiotics should be used only if clinical or laboratory evidence suggests bacterial infection. Use for viral illness or undifferentiated fever is inappropriate, subjects patients to drug complications without any benefit, and contributes to bacterial resistance. Certain bacterial infections (eg, abscesses, infections with foreign bodies) require surgical intervention and do not respond to antibiotics alone.

Spectrum of activity: Cultures and antibiotic sensitivity testing are essential for selecting a drug for serious infections. However, treatment must often begin before culture results are available, necessitating selection according to the most likely pathogens (empiric antibiotic selection). Whether chosen according to culture results or not, drugs with the narrowest spectrum of activity that can control the infection should be used. For empiric treatment of serious infections that may involve any one of several pathogens (eg, fever in neutropenic patients) or that may be due to multiple pathogens (eg, polymicrobial anaerobic infection), a broad spectrum of activity is desirable. The most likely pathogens and their susceptibility to antibiotics vary according to geographic location (within cities or even within a hospital) and can change from month to month.

For serious infections, combinations of antibiotics are often necessary because multiple species of bacteria may be present or because combinations act synergistically against a single species of bacteria. Synergism is usually defined as a more rapid and complete bactericidal action from a combination of antibiotics than occurs with either antibiotic alone. A common example is a cell wall-active antibiotic (eg, a β-lactam, vancomycin) plus an aminoglycoside.

Effectiveness: In vivo antibiotic effectiveness involves many factors, including

• Pharmacology (eg, absorption, distribution, concentration in fluids and tissues, protein binding, rate of metabolism or excretion)

• Pharmacodynamics (ie, the time course of antibacterial effects exerted by drug levels in blood and at the site of infection)

• Drug interactions or inhibiting substances

• Host defense mechanisms

[**Table 132-2.** Common Effects of Antibiotics on Other Drugs]

• In vitro killing power but usually only if the site of infection (eg, in meningitis or endocarditis) is resistant to treatment or if systemic host defenses are weak (eg, in neutropenic or other immunocompromised patients)

Bactericidal drugs kill bacteria in vitro. Bacteriostatic drugs slow or stop in vitro bacterial growth. These definitions are not absolute; bacteriostatic drugs may kill some bacteria, and bactericidal drugs may not kill all of the bacteria in vitro. More precise quantitative methods identify the minimum in vitro

concentration at which an antibiotic can inhibit growth (minimum inhibitory concentration, or MIC) or kill (minimum bactericidal concentration, or MBC).

The predominant determinant of bacteriologic response to antibiotics is the time that blood levels of the antibiotic exceed the MIC (time-dependence) or the peak blood level relative to MIC (concentration-dependence).

β-Lactams and vancomycin exhibit time-dependent bactericidal activity. Increasing their concentration above the MIC does not increase their bactericidal activity, and their in vivo killing is generally slow. In addition, because there is no or very brief residual inhibition of bacterial growth after concentrations fall below the MIC (postantibiotic effect, or PAE), β-lactams and vancomycin are most often effective when serum levels of free drug (drug not bound to serum protein) exceed the MIC for ≥ 50% of the time. Because ceftriaxone has a long serum half-life, free serum levels exceed the MIC of very susceptible pathogens for the entire 24-h dosing interval. However, for β-lactams that have serum half-lives of ≤ 2 h, frequent dosing or continuous infusion is required. For vancomycin, trough levels should be maintained at least at 10 to 15 μg/mL.

Aminoglycosides, fluoroquinolones, and daptomycin exhibit concentration-dependent bactericidal activity. Increasing their concentrations from levels slightly above the MIC to levels far above the MIC increases their rate of bactericidal activity and decreases the bacterial load. In addition, if concentrations exceed the MIC even briefly, aminoglycosides and fluoroquinolones have a PAE on residual bacteria; duration of PAE is also concentration-dependent. If PAEs are long, drug levels can be below the MIC for extended periods without loss of efficacy, allowing less frequent dosing. Consequently, aminoglycosides and fluoroquinolones are usually most effective as intermittent boluses that reach peak free serum levels ≥ 10 times the MIC of the bacteria.

Route: For many antibiotics, oral administration results in therapeutic blood levels nearly as rapidly as IV administration. However, IV administration is preferred in the following circumstances:

• Oral antibiotics cannot be tolerated (eg, because of vomiting).

• Oral antibiotics cannot be absorbed (eg, because of malabsorption after intestinal surgery).

• Intestinal motility is impaired (eg, because of opioid use).

• No oral formulation is available (eg, for aminoglycosides).

• Patients are critically ill, possibly impairing GI tract perfusion or making even the brief delay with oral administration detrimental.

Special populations: Doses and scheduling of antibiotics may need to be adjusted for the following:

• Infants

• The elderly

• Patients with renal failure (see
Table 132-3)

• Patients with hepatic insufficiency (most commonly for cefoperazone, ceftriaxone, chloramphenicol, clindamycin, metronidazole, nafcillin, rifabutin, and rifampin)

Pregnancy and breastfeeding affect choice of antibiotic. Penicillins, cephalosporins, and erythromycin are among the safest antibiotics during pregnancy; tetracyclines are contraindicated. Most antibiotics reach sufficient concentrations in breast milk to affect a breastfed baby, sometimes contraindicating their use in women who are breastfeeding.

Duration: Antibiotics should be continued until objective evidence of systemic infection (eg, fever,

symptoms, abnormal laboratory findings) is absent for several days. For some infections (eg, endocarditis, TB, osteomyelitis), antibiotics are continued for weeks or months to prevent relapse.

Complications: Complications of antibiotic therapy include superinfection by nonsusceptible bacteria or fungi and cutaneous, renal, hematologic, and GI adverse effects. Adverse effects frequently require stopping the causative drug and substituting another antibiotic to which the bacteria are susceptible; sometimes, no alternatives exist.

Antibiotic Resistance

Resistance to an antibiotic may be inherent in a particular bacterial species or may be acquired through mutations or acquisition of genes for antibiotic resistance that are obtained

[**Table 132-3.** Usual Doses of Commonly Prescribed Antibiotics]

[
Table 132-4. Common Mechanisms of Antibiotic Resistance]

from another organism. Different mechanisms for resistance are encoded by these genes (see Table 132-4). Resistance genes can be transmitted between 2 bacterial cells by the following mechanisms:

• Transformation (uptake of naked DNA from another organism)

• Transduction (infection by a bacteriophage)

• Conjugation (exchange of genetic material in the form of either plasmids, which are pieces of independently replicating extra-chromosomal DNA, or transposons, which are movable pieces of chromosomal DNA) Plasmids and transposons, which can rapidly disseminate resistance genes

Antibiotic use preferentially eliminates non-resistant bacteria, increasing the proportion of resistant bacteria that remain. Antibiotic use has this effect not only on pathogenic bacteria but also on normal flora; resistant normal flora can become a reservoir for resistance genes that can spread to pathogens.

Aminoglycosides

Aminoglycosides (see
Table 132-5) have concentration-dependent bactericidal activity. They bind to the 30S ribosome, thereby inhibiting bacterial protein synthesis.

Pharmacology

Aminoglycosides are poorly absorbed orally but are well absorbed from the peritoneum, pleural cavity, and joints (and should never be instilled in these body cavities) and from denuded skin. Aminoglycosides are usually given IV. Aminoglycosides are distributed well into ECF except for vitreous humor, CSF, respiratory secretions, and bile (particularly in patients with biliary obstruction). Intravitreous injection is required to treat endophthalmitis. Intraventricular injection is often required to reach intraventricular levels high enough to treat meningitis.

[**Table 132-5.** Aminoglycosides]

Aminoglycosides are excreted by glomerular filtration and have a serum half-life of 2 to 3 h; the half-life increases exponentially as the GFR falls (eg, in renal insufficiency, in the elderly).

Indications

Aminoglycosides are used for

• Serious gram-negative bacillary infections (especially those due to *Pseudomonas aeruginosa*)

Aminoglycosides are active against most gram-negative aerobic and facultative anaerobic bacilli but lack activity against anaerobes and most gram-positive bacteria, except for most staphylococci; however, some gram-negative bacilli and methicillin-resistant staphylococci are resistant.

Aminoglycosides that are active against *P. aeruginosa* include tobramycin (particularly), gentamicin, and amikacin. Streptomycin, neomycin, and kanamycin are not active against *P. aeruginosa*. Gentamicin and tobramycin have similar antimicrobial spectra against gram-negative bacilli, but tobramycin is more active against *P. aeruginosa*, and gentamicin is more active against *Serratia marcescens*. Amikacin is frequently active against gentamicin- and tobramycin-resistant pathogens.

Aminoglycosides are infrequently used alone, typically for plague and tularemia. They are usually used with a broad-spectrum β-lactam for severe infection suspected to be due to a gram-negative bacillary species. However, because of increasing aminoglycoside resistance, a fluoroquinolone can be substituted for the aminoglycoside in initial empiric regimens, or if the pathogen is found to be susceptible to the accompanying antibiotic, the aminoglycoside can be stopped after 2 to 3 days unless an aminoglycoside-sensitive *P. aeruginosa* is identified.

Gentamicin or, less commonly, streptomycin may be used with other antibiotics to treat endocarditis due to streptococci or enterococci. Enterococcal resistance to aminoglycosides has become a common problem. Because treatment of enterococcal endocarditis requires prolonged use of a potentially nephrotoxic and ototoxic aminoglycoside plus a bacterial cell wall-active drug (eg, penicillin, vancomycin) to achieve bactericidal synergy, the choice of aminoglycoside must be based on special in vitro susceptibility testing. Susceptibility only to high levels of aminoglycosides in vitro predicts synergy when low-dose aminoglycoside therapy is combined with a cell wall-active drug. If the strain is susceptible to high levels of gentamicin and streptomycin, gentamicin is preferred because serum levels can be readily determined and toxicity is less. High-level enterococcal resistance to gentamicin in vitro does not rule out susceptibility of these strains to high levels of streptomycin; in such cases, streptomycin should be used. Few therapeutic options are available for endocarditis due to enterococci that are resistant to high levels of gentamicin and streptomycin; no synergistic cell wall-active drug/aminoglycoside combination exists for endocarditis due to such strains, but long courses of a cell wall-active drug alone or combined with daptomycin or linezolid have had limited success.

Streptomycin has limited uses because of resistance and toxicity. It is used with other antibiotics to treat TB.

Because of toxicity, neomycin and kanamycin are limited to topical use in small amounts. Neomycin is available for eye, ear, oral, and rectal use and as a bladder irrigant. Oral neomycin is used topically against intestinal flora to prepare the bowel before surgery and to treat hepatic coma.

Contraindications

Aminoglycosides are contraindicated in patients who are allergic to them.

Use During Pregnancy and Breastfeeding

Aminoglycosides are in pregnancy category D (there is evidence of human risk, but clinical benefits may outweigh risk). Aminoglycosides enter breast milk but are not well absorbed orally. Thus, they are considered compatible with use during breastfeeding.

Adverse Effects

All aminoglycosides cause

• Renal toxicity (often reversible)

• Vestibular and auditory toxicity (often irreversible)

• Prolongation of effects of neuromuscular blockers

Symptoms and signs of vestibular damage are vertigo, nausea, vomiting, nystagmus, and ataxia.

Risk factors for renal, vestibular, and auditory toxicity are

• Frequent or very high doses

• Very high blood levels of the drug

• Long duration of therapy (particularly > 3 days)

• Older age

• A preexisting renal disorder

• Coadministration of vancomycin, cyclosporine, or amphotericin B

• For renal toxicity, coadministration of contrast agents

• For auditory toxicity, preexisting hearing problems and coadministration of loop diuretics

Patients receiving aminoglycosides for > 2 wk and those at risk of vestibular and auditory toxicity should be monitored with serial audiography. At the first sign of toxicity, the drug should be stopped (if possible), or dosing should be adjusted.

Aminoglycosides can prolong the effect of neuromuscular blockers (eg, succinylcholine, curare-like drugs) and worsen weakness in disorders affecting neuromuscular transmission (eg, myasthenia gravis). These effects are particularly likely when the drug is given too rapidly or serum levels are excessively high. The effects sometimes resolve more rapidly if patients are given neostigmine or IV Ca. Other neurologic effects include paresthesias and peripheral neuropathy.

Hypersensitivity reactions are uncommon. High oral doses of neomycin can cause malabsorption.

Dosing considerations: Because toxicity depends more on duration of therapeutic levels than on peak levels and because efficacy is concentration-dependent rather than timedependent, frequent doses are avoided. Once/day IV dosing is preferred for most indications except enterococcal endocarditis. IV aminoglycosides are given slowly (30 min for divided daily dosing or 30 to 45 min for once/day dosing).

In patients with normal renal function, once/day dosing of gentamicin or tobramycin is 5 mg/kg (7 mg/kg if patients are critically ill) q 24 h, and once/day dosing for amikacin is 15 mg/kg q 24 h. If patients respond to the higher dose of gentamicin clinically and renal

[
Table 132-6. Dosing for Aminoglycosides in Adults]

function continues to be normal, the once/day dose can be reduced to the lower dose after the first few days of treatment.

In critically ill patients, peak serum levels should be determined after the first dose. In all patients, peak and trough levels are measured after the 2nd or 3rd dose (when the daily dose is divided) or when therapy lasts > 3 days, as well as after the dose is changed. Serum creatinine is measured every 2 to 3 days, and if it is stable, serum aminoglycoside levels need not be measured again. Peak concentration is the level 60 min after an IM injection or 30 min after the end of a 30-min IV infusion. Trough levels are measured during the 30 min before the next dose.

Peak levels in serum of at least 10 times the MIC are desirable. Dosing is adjusted to ensure a therapeutic peak serum level (to facilitate concentration-dependent activity) and nontoxic trough levels

(see Table 132-6). In critically ill patients, who are likely to have expanded volumes of distribution and who are given higher initial doses, target peak serum levels are 16 to 24 μg/mL for gentamicin and tobramycin and 56 to 64 μg/mL for amikacin. For gentamicin and tobramycin, trough levels should be < 1 μg/mL at 18 to 24 h after the first dose with once/day dosing and between 1 and 2 μg/mL with divided daily dosing.

For patients with renal insufficiency, the loading dose is the same as that for patients with normal renal function; usually, the dosing interval is increased rather than the dose decreased. Guidelines for maintenance doses based on serum creatinine or creatinine clearance values are available (see Table 132-6), but they are not precise, and measurement of blood levels is preferred.

If patients are taking a high dose of a β-lactam (eg, piperacillin, ticarcillin) and an aminoglycoside, the high serum levels of the β-lactam can inactivate the aminoglycoside in vitro in serum specimens obtained to determine drug levels unless the specimen is assayed immediately or frozen. If patients with renal failure are concurrently taking an aminoglycoside and a high-dose β-lactam, the serum aminoglycoside level may be lower because interaction in vivo is prolonged.

Spectinomycin

Spectinomycin is a bacteriostatic antibiotic chemically related to the aminoglycosides. Spectinomycin binds to the 30S subunit of the ribosome, thus inhibiting bacterial protein synthesis. Its activity is restricted to gonococci. Spectinomycin is excreted by glomerular filtration.

Indications include

• Gonococcal urethritis

• Cervicitis

• Proctitis

Spectinomycin is not effective for gonococcal pharyngitis. It is reserved for patients who cannot be treated with ceftriaxone, cefpodoxime, cefixime, or a fluoroquinolone.

Adverse effects, including hypersensitivity reactions and fever, are rare.

β-Lactams

β-Lactams are antibiotics that have a β-lactam ring nucleus. Subclasses include

• Cephalosporins and cephamycins (cephems)

• Carbacephems (loracarbef)

• Penicillins

• Clavams

• Carbapenems

• Monobactams

All β-lactams bind to and inactivate enzymes required for bacterial cell wall synthesis.

Cephalosporins

Cephalosporins are bactericidal (see
Table 132-7). They inhibit enzymes in the cell wall of susceptible bacteria, disrupting cell synthesis.

Pharmacology

Cephalosporins penetrate well into most body fluids and the ECF of most tissues, especially when inflammation (which enhances diffusion) is present. However, the only cephalosporins that reach CSF levels high enough to treat meningitis are

• Ceftriaxone

• Cefotaxime

• Ceftazidime

• Cefepime

All cephalosporins penetrate poorly into ICF and the vitreous humor.

Most cephalosporins are excreted primarily in urine, so their doses must be adjusted in patients with renal insufficiency. Cefoperazone and ceftriaxone, which have significant biliary excretion, do not require such dose adjustment.

Indications

Cephalosporins are bactericidal for most of the following:

• Gram-positive bacteria

• Gram-negative bacteria

Cephalosporins are classified in generations (see Table 132-7). The 1st-generation

[**Table 132-7.** Cephalosporins*]

drugs are effective mainly against gram-positive organisms. Higher generations generally have expanded spectra against aerobic gram-negative bacilli. The 5th-generation cephalosporin ceftobiprole, which is not yet available in the US, is active against methicillin-resistant *Staphylococcus aureus*. Cephalosporins have the following limitations:

• Lack of activity against enterococci

• Lack of activity against methicillin-resistant staphylococci (except for ceftobiprole)

• Lack of activity against anaerobic gram-negative bacilli (except for cefotetan and cefoxitin)

First-generation cephalosporins: These drugs have excellent activity against

• Gram-positive cocci

Oral 1st-generation cephalosporins are commonly used for uncomplicated skin and soft-tissue infections, which are usually due to staphylococci and streptococci. Parenteral cefazolin is frequently used for endocarditis due to methicillin-sensitive *S. aureus* and for prophylaxis before cardiothoracic, orthopedic, abdominal, and pelvic surgery.

Second-generation cephalosporins and cephamycins: Second-generation cephalosporins are active against

• Gram-positive cocci

• Certain gram-negative bacilli

  Cephamycins are active against

• *Bacteroides* sp, including *B. fragilis*

These drugs may be slightly less active against gram-positive cocci than 1st-generation cephalosporins. Second-generation cephalosporins and cephamycins are often used for polymicrobial infections that include gram-negative bacilli and gram-positive cocci. Because cephamycins are active against *Bacteroides* sp, they can be used when anaerobes are suspected (eg, in intra-abdominal sepsis, decubitus ulcers, and diabetic foot infections). However, in some medical centers, these bacilli are no longer reliably susceptible to cephamycins.

Third-generation cephalosporins: These drugs are active against

• *Haemophilus influenzae* and some Entero-bacteriaceae (eg, *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*) that do not produce ampC β-lactamase or extended-spectrum β-lactamase (ESBL)

Ceftazidime and cefoperazone are also active against

• *Pseudomonas aeruginosa*

Some 3rd-generation cephalosporins have relatively poor activity against gram-positive cocci. Oral cefixime and ceftibuten have little activity against *S. aureus* and, if used for skin and soft-tissue infections, should be restricted to uncomplicated infections due to streptococci. These cephalosporins have many clinical uses, as does the 4th-generation cephalosporin (see Table 132-8).

Fourth-generation cephalosporin: The 4th-generation cephalosporin cefepime has activity against

• Gram-positive cocci (similar to cefotaxime)

• Gram-negative bacilli (enhanced activity), including *P. aeruginosa* (similar to ceftazidime), ESBL-producing *K. pneumoniae* and *E. coli*, and ampC β-lactamase-producing Enterobacteriaceae, such as *Enterobacter* sp

Fifth-generation cephalosporin: The 5th-generation cephalosporin ceftobiprole is active against

• Methicillin-resistant *S. aureus*

[**Table 132-8.** Some Clinical Uses of 3rd- and 4th-Generation Cephalosporins]

Contraindications

Cephalosporins are contraindicated in patients who are allergic to them or who have had an anaphylactic reaction to penicillins.

Use During Pregnancy and Breastfeeding

Cephalosporins are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not).

Cephalosporins enter breast milk and may alter bowel flora of the infant. Thus, use during breastfeeding is often discouraged.

Adverse Effects

Significant adverse effects include

• Hypersensitivity reactions (most common)

• *Clostridium difficile*-induced diarrhea (pseudomembranous colitis)

• Leukopenia

• Thrombocytopenia

• Positive Coombs' test (although hemolytic anemia is very uncommon)

Hypersensitivity reactions are the most common systemic adverse effects; rash is common, but immediate IgE-mediated urticaria and anaphylaxis are rare.

Cross-sensitivity between cephalosporins and penicillins is uncommon; cephalosporins can be given cautiously to patients with a history of delayed hypersensitivity to penicillin if necessary. However, cephalosporins should not be used in patients who have had an anaphylactic reaction to penicillin. Pain at the IM injection site and thrombophlebitis after IV use may occur.

Cefamandole (no longer available in the US), cefoperazone, and cefotetan may have a disulfiram-like effect when ethanol is ingested, causing nausea and vomiting. Cefamandole, cefoperazone, and cefotetan may elevate the PT/INR and PTT, an effect that is reversible with vitamin K.

Contraindications

Ceftriaxone is contraindicated as follows:

• Ceftriaxone IV must not be coadministered with Ca-containing IV solutions (including continuous Ca-containing infusions such as parenteral nutrition) in neonates ≤ 28 days because precipitation of ceftriaxone-Ca salt is a risk. Fatal reactions with ceftriaxone-Ca precipitates in the lungs and kidneys of neonates have been reported. In some cases, different infusion lines were used, and ceftriaxone and Ca-containing solutions were given at different times. To date, no intravascular or pulmonary precipitates have been reported in patients other than neonates who are treated with ceftriaxone and Ca-containing IV solutions. However, because an interaction between ceftriaxone and IV Ca-containing solutions is theoretically possible in patients other than neonates, ceftriaxone and Ca-containing solutions should not be mixed or given within 48 h of each other (based on 5 half-lives of ceftriaxone) —even via different infusion lines at different sites—to any patient regardless of age. No data on potential interaction between ceftriaxone and oral Ca-containing products or on interaction between IM ceftriaxone and Ca-containing products (IV or oral) are available.

• Ceftriaxone should not be given to hyperbilirubinemic and preterm neonates because in vitro, ceftriaxone can displace bilirubin from serum albumin, potentially triggering kernicterus.

Penicillins

Penicillins (see
Table 132-9) are bactericidal by unknown mechanisms but perhaps by activating autolytic enzymes that destroy the cell wall in some bacteria. Some bacteria produce β-lactamase, which inactivates the drug; this effect can be blocked by adding a β-lactamase inhibitor (clavulanate, sulbactam, or tazobactam). However, available β-lactamase inhibitors do not inhibit ampC β-lactamases, commonly produced by *Enterobacter, Serratia, Citrobacter, Providencia*, and *Morganella* spp or by *P. aeruginosa*, and these drugs may only partially inhibit ESBL produced by some *K. pneumoniae, E. coli*, and other Enterobacteriaceae.

[**Table 132-9.** Penicillins]

Pharmacology

Food does not interfere with absorption of amoxicillin, but penicillin G should be given 1 h before or 2 h after a meal. Amoxicillin has generally replaced ampicillin for oral use because amoxicillin is absorbed better, has fewer GI effects, and can be given less frequently.

Penicillins are distributed rapidly in the ECF of most tissues, particularly when inflammation is present.

All penicillins except nafcillin are excreted in urine and reach high levels in urine. Parenteral penicillin G is rapidly excreted (serum half-life 0.5 h), except for repository forms (the benzathine or procaine salt of penicillin G); these forms are intended for deep IM injection only and provide a tissue depot from which absorption takes place over several hours to several days. Benzathine penicillin reaches its peak level more slowly and is generally longeracting than procaine penicillin.

Indications

Penicillin G-like drugs (including penicillin V) are primarily used against

• Gram-positive bacteria

• Some gram-negative cocci (eg, meningococci)

A minority of gram-negative bacilli are also susceptible to large parenteral doses of penicillin G. Most staphylococci, most *Neisseria gonorrhoeae*, many anaerobic gram-negative bacilli, and about 30% of *H. influenzae* are resistant. Penicillin G is the drug of choice for syphilis and, with gentamicin, for endocarditis due to susceptible enterococci.

Benzathine penicillin G is available as pure benzathine penicillin, a mixture of equal amounts of benzathine and procaine penicillin G, and a mixture of 0.9 million units benzathine and 0.3 million units procaine penicillin G. Of the 3 products, only pure benzathine penicillin is recommended for treating syphilis and preventing rheumatic fever. Whether the mixture of equal amounts is effective in treating syphilis is unknown. Pure benzathine penicillin and the mixture of equal amounts are indicated for treating URIs and skin and soft-tissue infections caused by susceptible streptococci.

Amoxicillin and ampicillin: These drugs are more active against

• Enterococci

• Certain gram-negative bacilli, such as non-β-lactamase-producing *H. influenzae, E. coli*, and *P. mirabilis; Salmonella* sp; and *Shigella* sp

The addition of a β-lactamase inhibitor allows use against methicillin-sensitive staphylococci, *H. influenzae, N. gonorrhoeae, Moraxella catarrhalis, Bacteroides* sp, *E. coli*, and *K. pneumoniae*. Ampicillin is indicated primarily for infections typically caused by susceptible gram-negative bacteria:

• UTIs

• Meningococcal meningitis

• Biliary sepsis

• Respiratory infections

• *Listeria* meningitis

• Enterococcal infections

• Some typhoid fever and typhoid carriers

Penicillinase-resistant penicillins: These drugs are used primarily for

• Penicillinase-producing methicillin-sensitive *S. aureus*

These drugs are also used to treat some *S. pneumoniae*, group A streptococcal, and methicillin-sensitive coagulase-negative staphylococcal infections.

Broad-spectrum (antipseudomonal) penicillin: These drugs have activity against

• Bacteria susceptible to ampicillin

• Some strains of *Enterobacter* and *Serratia* spp

• Many strains of *P. aeruginosa*

Ticarcillin is less active against enterococci than piperacillin. The addition of a β-lactamase inhibitor enhances activity against β-lactamase-producing methicillin-sensitive *S. aureus, E. coli, K. pneumoniae, H. influenzae*, and gram-negative anaerobic bacilli, but not against gram-negative bacilli that produce ampC β-lactamase, and may only partially inhibit ESBL produced by some *K. pneumoniae*, *E. coli*, and other Enterobacteriaceae. Broad-spectrum penicillins exhibit synergy with aminoglycosides and are usually used with this class to treat *P. aeruginosa* infections.

Contraindications

Penicillins are contraindicated in patients who have had serious allergic reactions to them.

Use During Pregnancy and Breastfeeding

Penicillins are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not).

Penicillins enter breast milk in small amounts. Their use is usually considered compatible with breastfeeding.

Adverse Effects

Adverse effects include

• Hypersensitivity reactions, including rashes (most common)

Other adverse effects occur less commonly.

Hypersensitivity: Most adverse effects are hypersensitivity reactions:

• Immediate reactions: Anaphylaxis (which can cause death within minutes), urticaria and angioneurotic edema (in 1 to 5/10,000 injections), and death (in about 0.3/10,000 injections)

• Delayed reactions (in up to 8% of patients): Serum sickness, rashes (eg, macular, papular, morbilliform), and exfoliative dermatitis (which usually appears after 7 to 10 days of therapy)

Most patients who report an allergic reaction to penicillin do not react to subsequent exposure to penicillin. Although small, risk of an allergic reaction is about 10 times higher for patients who have had a previous allergic reaction. Many patients report adverse reactions to penicillin that are not truly allergic (eg, GI adverse effects, nonspecific symptoms). If patients have a vague or inconsistent history of penicillin allergy and taking alternative antibiotics is not effective or convenient, skin testing may be done (see p.). Desensitization may be attempted in patients with a positive skin test if there is no alternative to a penicillin-type drug. However, patients with a history of anaphylaxis to penicillin should not be given any β-lactam again (including for skin testing), except in very rare circumstances when no substitute can be found. In such cases, special precautions and desensitization regimens are required

Rashes: Rashes occur more often with ampicillin and amoxicillin than with other penicillins. Patients with infectious mononucleosis often develop a nonallergic rash, typically maculopapular, usually beginning between days 4 and 7 of treatment.

Other adverse effects: Penicillins can also cause

• CNS toxicity (eg, seizures) if doses are high, especially in patients with renal insufficiency

• Nephritis

• *C. difficile*-induced diarrhea (pseudomembranous colitis)

• Coombs'-positive hemolytic anemia

• Leukopenia

• Thrombocytopenia

Leukopenia seems to occur most often with nafcillin. Any penicillin used in very high IV doses can interfere with platelet function and cause bleeding, but ticarcillin is the most common cause, especially in patients with renal insufficiency.

Other adverse effects include pain at the IM injection site, thrombophlebitis when the same site is used repeatedly for IV injection, and, with oral formulations, GI disturbances. Rarely, black tongue, due to irritation of the glossal surface and keratinization of the superficial layers, occurs, usually when oral formulations are used. Ticarcillin in high doses may cause Na overload because ticarcillin is a disodium salt. Ticarcillin can also cause hypokalemic metabolic alkalosis because the large amount of nonabsorbable anion presented to the distal tubules alters H^+ ion excretion and secondarily results in K^+ loss.

Dosing Considerations

Because penicillins, except nafcillin, reach high levels in urine, doses must be reduced in patients with severe renal insufficiency. Probenecid inhibits renal tubular secretion of many penicillins, increasing blood levels. It is sometimes given to maintain high blood levels.

Other β-Lactams

Carbapenems (imipenem, meropenem, doripenem, and ertapenem) are parenteral bactericidal antibiotics that have an extremely broad spectrum. They are active against

• *H. influenzae*

• Anaerobes

• Most Enterobacteriaceae (including those that produce ampC β-lactamase and ESBL, although *P. mirabilis* tends to have higher imipenem MICs)

• Methicillin-sensitive staphylococci and streptococci, including *S. pneumoniae* (except possibly strains with reduced penicillin sensitivity)

Most *Enterococcus faecalis* and many *P. aeruginosa* strains, including those resistant to broad-spectrum penicillins and cephalosporins, are susceptible to imipenem, meropenem, and doripenem but are resistant to ertapenem. Carbapenems are active synergistically with aminoglycosides against *P. aeruginosa. E. faecium* and methicillin-resistant staphylococci are resistant.

Many multidrug-resistant hospital-acquired bacteria are sensitive only to carbapenems. However, expanded use of carbapenems has resulted in some carbapenem resistance.

Imipenem and meropenem penetrate into CSF when meninges are inflamed. Meropenem is used for gram-negative bacillary meningitis; imipenem is not used in meningitis because it may cause seizures. Most seizures occur in patients who have CNS abnormalities or renal insufficiency and who are given inappropriately high doses.

Aztreonam is a parenteral bactericidal antibiotic; it is as active as ceftazidime against

• Enterobacteriaceae that do not produce ampC β-lactamase or ESBL

• *P. aeruginosa*

Aztreonam is not active against anaerobes. Gram-positive bacteria are resistant to aztreonam (in contrast to cephalosporins). Aztreonam acts synergistically with aminoglycosides. Because the metabolic products of aztreonam differ from those of other β-lactams, cross-hypersensitivity is unlikely. Thus, aztreonam is used mainly for

• Severe aerobic gram-negative bacillary infections, including meningitis, in patients who have a serious β-lactam allergy but who nevertheless require β-lactam therapy

Other antibiotics are added to cover any suspected gram-positive cocci and anaerobes. The dose is reduced in renal failure.

Chloramphenicol

Chloramphenicol is primarily bacteriostatic. It binds to the 50S subunit of the ribosome, thereby inhibiting bacterial protein synthesis.

Pharmacology

Chloramphenicol is well absorbed orally. Parenteral therapy should be IV.

Chloramphenicol is distributed widely in body fluids, including CSF, and is excreted in urine. Because of hepatic metabolism, active chloramphenicol does not accumulate when renal insufficiency is present.

Indications

Chloramphenicol has a wide spectrum of activity against

• Gram-positive and gram-negative cocci and bacilli (including anaerobes)

• *Rickettsia, Mycoplasma, Chlamydia*, and *Chlamydophila* spp

Because of bone marrow toxicity, the availability of alternative antibiotics, and the emergence of resistance, chloramphenicol is no longer a drug of choice for any infection, except for

• Serious infections due to a few multidrug-resistant bacteria that remain susceptible to this antibiotic

However, when chloramphenicol has been used to treat meningitis caused by relatively penicillin-resistant pneumococci, outcomes have been discouraging, probably because chloramphenicol has poor bactericidal activity against these strains.

Contraindications

Chloramphenicol is contraindicated if another drug can be used instead.

Use During Pregnancy and Breastfeeding

Use of chloramphenicol during pregnancy results in fetal drug levels almost as high as maternal levels. Gray baby syndrome is a theoretical concern, particularly near term, but there is no clear evidence of fetal risk.

Chloramphenicol enters breast milk. Safety during breastfeeding has not been determined.

Adverse Effects

Adverse effects include

• Bone marrow depression (most serious)

• Nausea, vomiting, and diarrhea

• Gray baby syndrome (in neonates)

There are 2 types of bone marrow depression:

• Reversible dose-related interference with iron metabolism: This effect is most likely with high doses or prolonged treatment or in patients with a severe liver disorder.

• Irreversible idiosyncratic aplastic anemia: This anemia occurs in < 1/25,000 treated patients. It may not develop until after therapy is stopped. Chloramphenicol should not be used topically because small amounts may be absorbed and, rarely, cause aplastic anemia.

Hypersensitivity reactions are uncommon. Optic and peripheral neuritis may occur with prolonged use.

The neonatal gray baby syndrome, which involves hypothermia, cyanosis, flaccidity, and circulatory collapse, is often fatal. The cause is high blood levels, which occur because the immature liver cannot metabolize and excrete chloramphenicol. To avoid the syndrome, clinicians should not give infants ≤ 1 mo > 25 mg/kg/day initially, and doses should be adjusted based on blood levels of the drug.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic that has a unique mechanism of action. It binds to the bacterial cell membranes, causing rapid depolarization of the membrane due to K efflux and associated disruption of DNA, RNA, and protein synthesis; the result is rapid concentration-dependent bacterial death.

Indications

Daptomycin has activity against the following:

• Gram-positive bacteria (broad-spectrum activity)

• Multidrug-resistant gram-positive bacteria (because cross-resistance with other classes of antibiotics does not occur)

Daptomycin is used mainly for infections caused by

• Vancomycin- and methicillin-resistant *Staphylococcus aureus*

• Vancomycin-resistant enterococci

• Pneumococci with reduced penicillin sensitivity

However, methicillin-resistant *S. aureus* and vancomycin-resistant enterococci may become resistant during daptomycin therapy, resulting in relapsing or persistent infection.

Daptomycin is inferior to ceftriaxone for pneumonia, presumably because daptomycin can bind to pulmonary surfactant, reducing daptomycin's activity in the alveolar epithelial lining fluid.

Contraindications

Daptomycin is contraindicated in patients who have had an allergic reaction to it.

Use During Pregnancy and Breastfeeding

Daptomycin is in pregnancy category B (animal studies show no risk and human evidence is incomplete).

Whether daptomycin enters breast milk and is safe to use during breastfeeding is unknown.

Adverse Effects

Adverse effects include

• Eosinophilic pneumonia

• Myopathy

Chronic use may cause reversible organizing pneumonia with eosinophilic pulmonary infiltrates, presumably because daptomycin binds to pulmonary surfactant and thus accumulates in the alveolar spaces.

Skeletal myopathy due to daptomycin is reversible but seldom occurs with once/day dosing.

Dosing Considerations

Daptomycin is given parenterally once/day. Over 90% is bound to serum protein. Dosing is adjusted for renal failure. Because daptomycin can cause reversible skeletal myopathy, patients should be monitored for muscle pain or weakness, and serum creatine kinase levels should be checked weekly.

Fluoroquinolones

Fluoroquinolones (see Table 132-10) exhibit concentration-dependent bactericidal activity by inhibiting the activity of DNA gyrase and topoisomerase, enzymes essential for bacterial DNA replication. Fluoroquinolones are divided into 2 groups, based on antimicrobial spectrum and pharmacology:

• Older group: Ciprofloxacin, norfloxacin, and ofloxacin

• Newer group: Gemifloxacin, levofloxacin, and moxifloxacin

[**Table 132-10.** Fluoroquinolones]

Some newer fluoroquinolones have been withdrawn because of toxicity; they include trovafloxacin (because of severe hepatic toxicity) and gatifloxacin (because of hypoglycemia and hyperglycemia).

Pharmacology

Oral absorption is diminished by coadministration of cations (aluminum, Mg, Ca, zinc, and iron preparations). After oral and parenteral administration, fluoroquinolones are widely distributed in most extracellular and intracellular fluids and are concentrated in the prostate, lungs, and bile.

Most fluoroquinolones are metabolized in the liver and excreted in urine, reaching high levels in urine. Moxifloxacin is eliminated primarily in bile.

Indications

Fluoroquinolones are active against the following:

• *Neisseria* sp

• *Haemophilus influenzae*

• *Moraxella catarrhalis*

• *Mycoplasma* sp

• *Chlamydia* sp

• *Chlamydophila* sp

• *Legionella* sp

• Enterobacteriaceae

• *Pseudomonas aeruginosa* (particularly ciprofloxacin)

• *Mycobacterium tuberculosis*

• Some atypical mycobacteria

• Methicillin-sensitive staphylococci

Nosocomial methicillin-resistant staphylococci are usually resistant. Older fluoroquinolones have poor activity against streptococci and anaerobes. Newer fluoroquinolones have reliable activity against streptococci (including *Streptococcus pneumoniae* with reduced penicillin sensitivity) and some anaerobes. As use has increased, resistance, particularly to older fluoroquinolones, is developing among Enterobacteriaceae, *P. aeruginosa, S. pneumoniae*, and *Neisseria* sp. Nonetheless, fluoroquinolones have many clinical uses (see Table 132-11).

Fluoroquinolones are no longer recommended for treatment of gonorrhea in the US because of increasing resistance.

Contraindications

Contraindications include

• Previous allergic reaction to the drugs

• Certain disorders that predispose to arrhythmias (eg, QT-interval prolongation, uncorrected hypokalemia or hypomagnesemia, significant bradycardia)

• Use of drugs known to prolong the QT interval or to cause bradycardia (eg, metoclopramide, cisapride, erythromycin, clarithromycin, classes Ia and III antiarrhythmics, tricyclic antidepressants)

Fluoroquinolones have traditionally been considered to be contraindicated in children because they may cause cartilage lesions if growth plates are open. However, some experts, who challenge this view

because evidence is weak, have recommended prescribing fluoroquinolones as a 2nd-line antibiotic and restricting use to a few specific situations, including *P. aeruginosa* infections in patients with cystic fibrosis, prophylaxis and treatment of bacterial infections in immunocompromised patients, life-threatening multiresistant bacterial infections in neonates and infants, and *Salmonella* or *Shigella* GI tract infections.

Use During Pregnancy and Breastfeeding

Fluoroquinolones are in pregnancy category C (animal studies show some risk, evidence in human and animal studies is inadequate, but clinical benefit sometimes exceeds risk).

[**Table 132-11.** Some Clinical Uses of Fluoroquinolones]

Fluoroquinolones enter breast milk. Use during breastfeeding is not recommended.

Adverse Effects

Serious adverse effects are uncommon; main concerns include the following:

• Upper GI adverse effects occur in about 5% of patients because of direct GI irritation and CNS effects.

• CNS adverse effects (eg, mild headache, drowsiness, insomnia, dizziness, mood alteration) occur in < 5%. NSAIDs may enhance the CNS stimulatory effects of fluoroquinolones. Seizures are rare, but fluoroquinolones should not be used in patients with CNS disorders.

• Tendinopathy, including rupture of the Achilles tendon, may occur even after short-term use of fluoroquinolones.

• QT-interval prolongation can occur, potentially leading to ventricular arrhythmias and sudden cardiac death.

• Fluoroquinolone use has been strongly associated with *Clostridium difficile*-associated diarrhea (pseudomembranous colitis), especially that due to the hypervirulent *C. difficile* ribotype 027.

Diarrhea, leukopenia, anemia, and photosensitivity are uncommon. Rash is uncommon unless gemifloxacin is used for > 1 wk and is more likely to develop in women < 40. Nephrotoxicity is rare.

Dosing Considerations

Dose reduction, except for moxifloxacin, is required for patients with renal insufficiency. Older fluoroquinolones are normally given twice/day; newer ones and an extended-release form of ciprofloxacin are given once/day.

Ciprofloxacin raises theophylline levels, sometimes resulting in theophylline-related adverse effects.

Lincosamides, Oxazolidinones, and Streptogramins

Lincosamides (clindamycin), oxazolidinones (linezolid), streptogramins (dalfopristin [streptogramin A] and quinupristin [streptogramin B]) are grouped together because they have a similar mode of antibacterial action and similar antibacterial spectra. Macrolides (see p. 1212) and the ketolide telithromycin (see p. 1214) may be included with this group for similar reasons. All inhibit protein synthesis by binding to the 50S ribosomal subunit. Cross-resistance occurs among the following antibiotics because they bind to the same target:

• Macrolides

• Clindamycin

• Quinupristin

• Telithromycin (to some extent)

However, cross-resistance does not occur between these antibiotics and dalfopristin and linezolid, which bind to different targets on the 50S ribosomal subunit.

Lincosamides

Clindamycin is primarily bacteriostatic. It binds to the 50S subunit of the ribosome, thus inhibiting bacterial protein synthesis.

Pharmacology

Clindamycin is absorbed well orally and can be given parenterally. Clindamycin diffuses well into body fluids except CSF; it is concentrated in phagocytes. Most of the drug is metabolized; metabolites are excreted in bile and urine.

Indications

The spectrum of activity for clindamycin is similar to that of the macrolide erythromycin (see Table 132-13 on p. 1213) except that clindamycin is

• Effective for infections due to anaerobes (particularly *Bacteroides* sp, including *B. fragilis*), community-acquired methicillin-resistant *Staphylococcus aureus*, and macrolide-resistant, clindamycin-susceptible *Streptococcus pneumoniae*

• Not reliably active against mycoplasmas, chlamydiae, *Chlamydophila* sp, and legionellae

Aerobic gram-negative bacilli and enterococci are resistant.

Clindamycin is usually used for anaerobic infections; however, clindamycin resistance has emerged among these organisms in some regions. Because these infections often also involve aerobic gram-negative bacilli, additional antibiotics are also used. Clindamycin is part of combination therapy for the following:

• Infections caused by toxigenic streptococci (because clindamycin decreases the bacteria's toxin production)

• Cerebral toxoplasmosis

• Babesiosis

• Falciparum malaria

• *Pneumocystis jirovecii* pneumonia

Clindamycin can be used for infections (eg, skin and soft-tissue infections) in communities where community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is common; whether clindamycin is useful depends on local resistance patterns.

Clindamycin can be used for infections due to clindamycin- and erythromycin-susceptible strains. However, some CA-MRSA strains are clindamycin-susceptible and erythromycin-resistant; erythromycin resistance in these strains may be due to an active efflux mechanism or to erythromycin-inducible modification of the ribosomal target. If the infecting strain of clindamycin-susceptible CA-MRSA is resistant to erythromycin because of the efflux mechanism, patients can be expected to respond to clindamycin. However, if the strain is erythromycin-resistant because of erythromycin-inducible ribosomal target modification, patients may not respond clinically to clindamycin because certain mutants can emerge during clindamycin therapy; these mutants are resistant to clindamycin and erythromycin because

of constitutive modification of the ribosomal target. (Constitutive means that resistance is always present regardless of whether an inducer, such as erythromycin, is present.)

Erythromycin resistance due to efflux can be differentiated from that due to inducible ribosomal target modification with a commonly used double disk diffusion assay (D test). A clindamycin disk is placed at a standard distance from an erythromycin disk on an agar plate streaked with a standard inoculum of the CA-MRSA strain in question. Zone of growth inhibition (shaped like the letter "D") around the clindamycin disk, with a flattened zone nearest the erythromycin disk indicates inducible ribosomal resistance. Patients who have moderate to severe infection with an inducible ribosomal-resistant CA-MRSA strain and a positive D test should not be treated with clindamycin.

Clindamycin cannot be used for CNS infections (other than cerebral toxoplasmosis) because penetration into the brain and CSF is poor.

Topical clindamycin is used for acne.

Contraindications

Clindamycin is contraindicated in patients who have had an allergic reaction to it or have a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

Use During Pregnancy and Breastfeeding

Clindamycin is in pregnancy category B (animal studies show no risk but human evidence is inadequate, or animal studies show risk and human studies do not).

Clindamycin enters breast milk. Use during breastfeeding is not recommended.

Adverse Effects

The main adverse effect is

• *Clostridium difficile*-associated diarrhea (pseudomembranous colitis)

Clindamycin, penicillins, cephalosporins, and, most recently, fluoroquinolones have been associated with *C. difficile*-associated diarrhea. Clindamycin has been associated with *C. difficile*-associated diarrhea in up to 10% of patients regardless of route, including topical.

Hypersensitivity reactions may occur. If not swallowed with water, clindamycin may cause esophagitis.

Dosing Considerations

Dose adjustments are not required for renal failure. Clindamycin is given q 6 to 8 h.

Oxazolidinones

Linezolid has activity against the following:

• Streptococci

• Enterococci (*Enterococcus faecalis* and *E. faecium*)

• Staphylococci, including strains resistant to other classes of antibiotics

• Mycobacteria

• Anaerobes, such as *Fusobacterium, Prevotella, Porphyromonas*, and *Bacteroides* spp and peptostreptococci

Contraindications

Linezolid is contraindicated in patients with a prior allergic reaction to it.

Linezolid is a reversible, nonselective monamine oxidase inhibitor (MAOI). Thus, linezolid, when used with drugs that have serotonergic activity (eg, SSRIs, MAOIs, tricyclic antidepressants, L-tryptophan, amphetamines, lithium), has the potential for causing serotonin syndrome, a hyperserotonergic state characterized by mental status changes, neurologic abnormalities, and autonomic instability.

Linezolid is contraindicated in the following patients unless they are carefully observed for symptoms and signs of serotonin syndrome:

• Those who have taken MAO inhibitors (eg, phenelzine, isocarboxazid), serotonin reup-take inhibitors, tricyclic antidepressants, serotonin 1B,1D receptor agonists (triptans), meperidine, or buspirone within 2 wk

• Those with carcinoid syndrome

Linezolid should not be given to the following patients unless they are monitored for potential increases in BP:

• Those taking any of the following: sympathomimetic drugs (eg, pseudoephedrine), vasopressors (eg, epinephrine, norepinephrine), dopaminergic drugs (eg, dopamine, dobutamine)

• Those with uncontrolled hypertension

• Those with thyrotoxicosis

• Those with a pheochromocytoma

Use During Pregnancy and Breastfeeding

Linezolid is in pregnancy category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes exceeds risk).

Whether linezolid is excreted in breast milk or is safe to use during breastfeeding is unknown.

Adverse Effects

Adverse effects include

• Reversible myelosuppression

• Irreversible peripheral neuropathy

• Reversible optic neuropathy

• Serotonin syndrome

Adverse effects are minimal, although reversible myelosuppression, including thrombocytopenia, leukopenia, and anemia, occurs in about 3% of patients, usually when therapy is used > 2 wk. Consequently, CBC is monitored weekly, especially when therapy lasts > 2 wk. Peripheral and optic neuropathy may occur with prolonged use, and patients taking long-term linezolid therapy should be closely monitored for these disorders.

Streptogramins

Quinupristin and dalfopristin are semisynthetic derivatives of pristinamycin, a naturally occurring streptogramin. Quinupristin/dalfopristin (Q/D) is given together in a fixed 30/70 combination; this combination has synergistic bactericidal activity against the following:

• Streptococci and staphylococci, including strains resistant to other antibiotic classes

• Some gram-negative anaerobic bacilli

• *Clostridium perfringens*

• *Peptostreptococcus* sp

• Atypical respiratory pathogens (*Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila*)

Q/D inhibits *E. faecium*, including vancomycin-resistant strains. *E. faecalis* is resistant.

Q/D is given via a central IV catheter because phlebitis frequently occurs when Q/D is given via a peripheral vein. Up to 30% of patients develop significant myalgias.

Dosage reduction is required for severe hepatic insufficiency but not for renal insufficiency.

Q/D may inhibit drugs that are metabolized by the cytochrome P-450 (CYP450) 3A4 isoenzyme system.

Macrolides

Macrolides (see
Table 132-12) are primarily bacteriostatic; by binding to the 50S subunit of the ribosome, they inhibit bacterial protein synthesis.

Pharmacology

Dirithromycin is a prodrug that is converted to its active form during intestinal absorption. Except for telithromycin, macrolides are relatively poorly absorbed orally. Food has the following effects on absorption:

• For dirithromycin and extended-release clarithromycin, increased absorption

• For immediate-release clarithromycin tablet or suspension, no effect

• For azithromycin capsules and erythromycin (including base and stearate formulations), decreased absorption

All macrolides diffuse well into body fluids, except CSF, and are concentrated in phagocytes. Excretion is mainly in bile.

Indications

Macrolides are active against

• Aerobic and anaerobic gram-positive cocci, except for most enterococci, many *Staphylococcus aureus* strains (especially methicillin-resistant strains), and some *Streptococcus pneumoniae* and *S. pyogenes* strains

• *Mycoplasma pneumoniae*

• *Chlamydia trachomatis*

• *Chlamydophila pneumoniae*

• *Legionella* sp

[**Table 132-12.** Macrolides]

• *Corynebacterium diphtheriae*

• *Campylobacter* sp

• *Treponema pallidum*

• *Propionibacterium acnes*

• *Borrelia burgdorferi*

Bacteroides fragilis is resistant. Clarithromycin and azithromycin have enhanced activity against *Haemophilus influenzae* and activity against *Mycobacterium avium* complex.

Macrolides have been considered the drug of choice for group A streptococcal and pneumococcal infections when penicillin cannot be used. However, pneumococci with reduced penicillin sensitivity are often resistant to macrolides, and in some communities, up to 20% of *S. pyogenes* are macrolide-resistant. Because they are active against atypical respiratory pathogens, they are often used empirically for lower respiratory tract infections, but another drug is often necessary to cover macrolide-resistant pneumococci. Macrolides have other clinical uses (see Table 132-13). Macrolides are not used to treat meningitis.

Contraindications

Macrolides are contraindicated in patients who have had an allergic reaction to them.

Concomitant administration of macrolides with astemizole, cisapride, pimozide, or terfenadine is contraindicated. Postmarketing surveillance has reported cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, torsades de pointes) when clarithromycin or erythromycin was coadministered with astemizole, cisapride, pimozide, or terfenadine; this effect was most likely due to inhibition of metabolism of these drugs by erythromycin and clarithromycin. Deaths have been reported.

Use During Pregnancy and Breastfeeding

Erythromycin and azithromycin are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Erythromycin is considered safer because clinical use has been much more extensive.

Clarithromycin is in category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk).

Erythromycin is considered compatible with breastfeeding. Safety of other macrolides during breastfeeding is unknown.

Adverse Effects

Main concerns include

• GI disturbances (mainly with erythromycin)

• QT-interval prolongation by erythromycin

• Inhibition of hepatic metabolism, leading to numerous drug interactions

Erythromycin commonly causes dose-related GI disturbances, including nausea, vomiting, abdominal cramps, and diarrhea; disturbances are less common with clarithromycin and azithromycin. Taking the drug with food may help

[**Table 132-13.** Some Clinical Uses of Macrolides]

decrease GI disturbances. Erythromycin may cause dose-related tinnitus, dizziness, and reversible hearing loss. Cholestatic jaundice occurs most commonly with erythromycin estolate. Jaundice usually appears after 10 days of use, primarily in adults but can occur earlier if the drug has been given previously. Erythromycin is not given IM because it causes severe pain; when given IV, it may cause phlebitis or pain. Hypersensitivity reactions are rare.

Erythromycin causes QT-interval prolongation and predisposes to ventricular tachyarrhythmia, especially in women, in patients who have QT-interval prolongation or electrolyte abnormalities, and in patients taking another drug that may prolong the QT interval.

Dosing Considerations

For azithromycin and dirithromycin, no dosage adjustment is required for renal insufficiency.

Erythromycin and, to some extent, clarithromycin interact with numerous drugs because they inhibit hepatic metabolism via the cytochrome P-450 (CYP450) system. Azithromycin is the least likely to interact with other drugs. Interactions may occur when erythromycin or clarithromycin are taken with the following:

• Warfarin: Further elevation of the PT/INR

• Lovastatin and simvastatin: Rhabdomyolysis

• Midazolam and triazolam: Somnolence

• Theophylline: Nausea, vomiting, and seizures

• Tacrolimus, cyclosporine, and ergot alkaloids: Elevated serum levels of these drugs

Telithromycin

Telithromycin is a ketolide antibiotic. Ketolides are chemically related to macrolides and inhibit bacterial ribosomal protein synthesis without inducing resistance to macrolides, clindamycin, or streptogramins.

Telithromycin is rapidly absorbed orally with or without food and is metabolized primarily in the liver.

Indications

Telithromycin is active against erythromycin-susceptible staphylococci and streptococci and multidrug-resistant *S. pneumoniae*. Telithromycin is also active against erythromycin-susceptible enterococci, *Bordetella pertussis*, *H. influenzae, Helicobacter pylori, Moraxella catarrhalis, M. pneumoniae, C. pneumoniae*, and *Legionella, Prevotella*, and *Peptostreptococcus* spp.

Because of safety concerns, telithromycin is recommended only for the treatment of adults ≥ 18 yr with community acquired mild to moderate pneumonia due to the following:

• *S. pneumoniae* (including multidrug-resistant strains, ie, penicillin-resistant *S. pneumoniae*; isolates resistant to ≥ 2 of the following: penicillin, 2nd-generation cephalosporins [eg, cefuroxime], macrolides, tetracyclines, trimethoprim/sulfamethoxazole)

• *H. influenzae*

- *M. catarrhalis*

- *C. pneumoniae*

- *M. pneumoniae*

Contraindications

Contraindications include

- Previous allergic reaction to telithromycin or any macrolide

- Previous hepatitis or jaundice after taking telithromycin or a macrolide

- Concurrent use of pimozide or cisapride because of cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, torsades de pointes)

- Myasthenia gravis because telithromycin may exacerbate symptoms and fatal respiratory failure has occurred in patients with this disorder

Use During Pregnancy and Breastfeeding

Telithromycin is in pregnancy category C because animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk.

Safety of telithromycin during breastfeeding is unknown.

Adverse Effects

Adverse effects include

- GI disturbances

- QT-interval prolongation

- Severe hepatitis

Diarrhea, nausea, vomiting, and dizziness are the most common adverse effects. Prolongation of the QT interval, hyperbilirubinemia, elevation of liver enzymes, transient loss of consciousness (sometimes associated with vagal syndrome), and visual disturbances (particularly a slowed ability to accommodate and to release accommodation) are less common. Severe hepatotoxicity, which may require liver transplantation and which may be fatal, may occur.

Cross-sensitivity with macrolides can occur.

Dosing Considerations

Telithromycin inhibits cytochrome P-450 (CYP450) 3A4, increasing levels of the following drugs:

- Digoxin: Digoxin adverse effects or serum levels should be monitored.

- Ergot alkaloids: Concomitant use should be avoided.

- Benzodiazepines: Concomitant use requires caution.

- Metoprolol: Concomitant use in patients with heart failure requires caution.

• Statins: Concomitant use of simvastatin, lovastatin, or atorvastatin (but not pravastatin or fluvastatin) should be avoided.

• Cisapride: Concomitant use is contraindicated.

• Pimozide: Concomitant use is contraindicated.

• Sirolimus

• Tacrolimus

CYP3A4 inducers such as rifampin, phenytoin, carbamazepine, and phenobarbital decrease levels of telithromycin; the CYP3A4 inhibitors itraconazole and ketoconazole increase levels of telithromycin. Telithromycin decreases absorption of sotalol.

Metronidazole

Metronidazole is bactericidal. It enters bacterial cell walls and interrupts DNA.

Pharmacology

Oral metronidazole is absorbed well. It is usually given IV only if patients cannot be treated orally. It is distributed widely in body fluids and penetrates into CSF, resulting in high concentrations. Metronidazole is metabolized presumably in the liver and excreted mainly in urine, but elimination is not decreased in patients with renal insufficiency.

Indications

Metronidazole is active against

• All obligate anaerobic bacteria (it is inactive against facultative anaerobic and aerobic bacteria)

• Certain protozoan parasites (eg, *Trichomonas vaginalis, Entamoeba histolytica, Giardia intestinalis [lamblia]*)

Metronidazole is used primarily for infections caused by obligate anaerobes, often with other antimicrobials. Metronidazole is the drug of choice for bacterial vaginosis. The drug has other clinical uses (see
Table 132-14).

Contraindications

Metronidazole is contraindicated in patients who have had an allergic reaction to it.

Use During Pregnancy and Breastfeeding

Metronidazole is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Nonetheless, metronidazole should be avoided during the 1st trimester because mutagenicity is a concern.

[**Table 132-14.** Some Clinical Uses of Metronidazole]

Metronidazole enters breast milk; use during breastfeeding is not recommended.

Adverse Effects

Adverse effects include

• GI disturbances

• CNS effects and peripheral neuropathy

• Disulfiram-like reaction

Nausea, vomiting, headache, seizures, syncope, other CNS effects, and peripheral neuropathy can occur; rash, fever, and reversible neutropenia have been reported. Metronidazole can cause a metallic taste and dark urine. A disulfiram-like reaction may occur if alcohol is ingested within 7 days of use.

Dosing Considerations

Metronidazole doses are not decreased in patients with renal failure but are usually decreased 50% in patients with significant liver disease.

Metronidazole inhibits metabolism of warfarin and may increase its anticoagulant effect.

Mupirocin

Mupirocin inhibits bacterial RNA and protein synthesis. It is available only as a 2% topical preparation, which is bactericidal against staphylococci and β-hemolytic streptococci. Systemic absorption of topical mupirocin is negligible.

Mupirocin is used for impetigo and for minor superficial secondarily infected skin lesions. Mupirocin can also eradicate *Staphylococcus aureus* nasal carriage, although relapse rates may be high. Chronic therapy leads to mupirocin-resistant staphylococci.

Mupirocin is nontoxic but, when applied to denuded skin or mucous membranes, may cause itching and burning.

Nitrofurantoin

Nitrofurantoin is bactericidal; the exact mechanism is unknown.

Nitrofurantoin is available only for oral use.

Pharmacology

After a single dose, serum drug levels are very low, but urine drug levels are therapeutic.

Indications

Nitrofurantoin is active against common uropathogens, such as

• *Escherichia coli*

• *Staphylococcus saprophyticus*

• *Enterococcus faecalis*

E. faecium, including vancomycin-resistant strains, and *Klebsiella* and *Enterobacter* sp are less susceptible. Most strains of *Proteus*, *Providencia*, *Morganella*, *Serratia*, *Acinetobacter*, and *Pseudomonas* spp are resistant. There is no cross-resistance with other antibiotic classes.

Nitrofurantoin is used only for

• Treatment or prophylaxis of uncomplicated UTI

In women with recurrent UTIs, it may decrease the number of episodes.

Contraindications

Contraindications to nitrofurantoin use include

• Previous allergic reaction to it

• Renal insufficiency (creatinine clearance < 60 L/min)

• Age < 1 mo

Use During Pregnancy and Breastfeeding

Nitrofurantoin is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Nonetheless, nitrofurantoin is contraindicated at term and during labor or delivery because it interferes with immature enzyme systems in RBCs of neonates, damaging the cells and resulting in hemolytic anemia.

Nitrofurantoin enters breast milk and is contraindicated during the first month of breast-feeding.

Adverse Effects

Adverse effects include

• GI disturbances

• Pulmonary toxicity

• Peripheral neuropathy

• Hemolytic anemia

• Hepatic toxicity

Common adverse effects are nausea and vomiting, which are less likely with the macrocrystalline form. Fever, rash, acute hypersensitivity pneumonitis (accompanied by fever and eosinophilia), and chronic progressive pulmonary interstitial fibrosis may occur. Paresthesias may result and may be followed by a severe ascending motor and sensory polyneuropathy if the drug is continued, especially in patients with renal failure. Leukopenia and hepatic toxicity (acute cholestatic or chronic active hepatitis) have been reported, and hemolytic anemia can occur in patients with G6PD deficiency and in infants < 1 mo. Chronic pulmonary and hepatic reactions occur when the drug is used for > 6 mo.

Polypeptides

Polypeptide antibiotics disrupt bacterial cell walls (see Table 132-15).

Bacitracin is a polypeptide antibiotic that inhibits cell wall synthesis and is active against gram-positive bacteria.

Colistin (polymyxin E) and polymyxin B are cationic polypeptide antibiotics that disrupt the outer bacterial cell membrane by binding to the anionic outer membrane, which contains lipopolysaccharide (endotoxin), and thereby neutralizing the bacteria's toxicity.

Colistin methane sulfonate (colistimethate sodium [CMS]) is a parenteral preparation of a prodrug that is transformed in blood and urine to colistin. CMS is less toxic than colistin.

Polypeptides are usually used topically; systemic absorption is negligible.

Indications

Polymyxin B and colistin have rapid concentration-dependent bactericidal activity against

• Most facultative and aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* and *Acinetobacter* sp

These drugs are not active against *Proteus, Providencia, Burkholderia*, *and Serratia* spp and some obligate anaerobes, including *Bacteroides fragilis* and gram-positive bacteria. Development of resistance is uncommon.

Polypeptides are used for several types of infections (see Table 132-16).

Contraindications

All polypeptides are contraindicated in patients who have had an allergic reaction to them. CMS and polymyxin B should not be given simultaneously with drugs that block neuromuscular transmission or are nephrotoxic (eg, aminoglycosides, curare-like drugs).

Use During Pregnancy and Breastfeeding

Bacitracin may pose minimal risk during pregnancy and breastfeeding because systemic absorption is minimal; however, safety has not been established.

Polymyxin B is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not).

[**Table 132-15.** Polypeptides]

Colistin is in pregnancy category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk); this drug crosses the placenta. Whether use during breastfeeding is safe is unknown.

Adverse Effects

Adverse effects include

• Nephrotoxicity

• Central and peripheral neurotoxicity

Polymyxins are nephrotoxic. CMS and polymyxin B may cause circumoral and extremity paresthesias, vertigo, slurred speech, and muscle weakness and respiratory difficulty due to neuromuscular blockade, especially in patients with renal insufficiency.

Rifamycins

The rifamycins are bactericidal and inhibit bacterial DNA-dependent RNA polymerase, suppressing RNA synthesis (see Table 132-17).

Rifampin and Rifabutin

Rifampin and rifabutin have similar pharmacology, antimicrobial spectra, and adverse effects.

Pharmacology

Oral absorption is good, producing wide distribution in body tissues and fluids, including CSF. Rifampin is concentrated in polymorpho-nuclear granulocytes and macrophages, facilitating clearance of bacteria from abscesses. It is metabolized in the liver and eliminated in bile and, to a much lesser extent, in urine.

Indications

Rifampin is active against

• Most gram-positive and some gram-negative bacteria

• *Mycobacterium* sp

Resistance develops rapidly, so rifampin is rarely used alone. Rifampin is used with other antibiotics for

• TB (see p.)

• Atypical mycobacterial infection (rifampin is active against many nontuberculous mycobacteria, but rapidly growing mycobacteria, such as *M. fortuitum* or *M. chelonae*, are naturally resistant)

• Leprosy (with dapsone with or without clofazimine)

• Staphylococcal infections, including osteomyelitis, prosthetic valve endocarditis, and

[**Table 132-16.** Some Clinical Uses of Polypeptides]

infections involving foreign bodies such as a prosthetic joint (with other antistaphylococcal antibiotics)

• *Legionella* infections (older data suggest better outcomes for rifampin when used with erythromycin; use of rifampin with azithromycin or a fluoroquinolone offers no advantage)

• Pneumococcal meningitis when organisms are susceptible to rifampin (with vancomycin

[**Table 132-17.** Rifamycins]

with or without ceftriaxone or cefotaxime for ceftriaxone- or cefotaxime-resistant organisms [MIC > 4 µg/mL]) or when expected clinical or microbiologic response is delayed

Rifampin can be used alone for prophylaxis of close contacts of patients with meningococcal or *Haemophilus influenzae* type b meningitis.

Rifabutin and rifampin are equally efficacious in regimens for TB in HIV-positive and HIV-negative patients.

Rifabutin is more active than rifampin against *M. avium* complex and is used preferentially in multidrug regimens for these infections, but otherwise, rifampin is preferred.

Contraindications

Rifampin and rifabutin are contraindicated in patients who have had an allergic reaction to them.

Use During Pregnancy and Breastfeeding

Rifabutin is in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Safety during breast-feeding is unknown.

Rifampin is in pregnancy category C (animal studies show some risk [in this case, teratogenicity], evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk). The drug crosses the placenta. Still, if risk of maternal TB is moderate or high, treatment is thought to be less harmful for the fetus than untreated maternal TB and is thus recommended. Because of potential tumorigenicity shown in animal studies, a decision to stop breastfeeding or to stop the drug should be made, depending on the importance of the drug to the mother.

Adverse Effects

Adverse effects include

• Hepatitis (most serious)

• GI disturbances

• CNS effects

• Myelosuppression

Hepatitis occurs much more often when isoniazid or pyrazinamide is used concurrently with rifampin. During the first week of therapy, rifampin may cause a transient rise in unconjugated serum bilirubin, which results from competition between rifampin and bilirubin for excretion and which is not in itself an indication for interrupting treatment.

CNS effects may include headache, drowsiness, ataxia, and confusion. Rash, fever, leukopenia, hemolytic anemia, thrombocytopenia, interstitial nephritis, acute tubular necrosis, renal insufficiency, and interstitial nephritis are generally considered to be hypersensitivity reactions and occur when therapy is intermittent or when treatment is resumed after interruption of a daily dosage regimen; they are reversed when rifampin is stopped.

Less serious adverse effects are common; they include heartburn, nausea, vomiting, and diarrhea. Rifampin colors urine, saliva, sweat, sputum, and tears red-orange.

Dosing Considerations

If patients have a liver disorder, liver function tests should be done before rifampin therapy is started and every 2 to 4 wk during therapy, or an alternate drug should be used. Dose adjustments are unnecessary for renal insufficiency.

Rifampin interacts with many drugs because it is a potent inducer of hepatic cytochrome P-450 (CYP450) microsomal enzymes. Rifampin accelerates elimination and thereby may decrease the effectiveness of the following drugs: ACE inhibitors, atovaquone, barbiturates, β-blockers, Ca channel blockers, chloramphenicol, clarithromycin, oral and systemic hormone contraceptives, corticosteroids, cyclosporine, dapsone, digoxin, doxycycline, fluconazole, haloperidol, itraconazole, ketoconazole, the nonnucleoside reverse transcriptase inhibitors delavirdine and nevirapine, opioid analgesics, phenytoin, protease inhibitors, quinidine, sulfonylureas, tacrolimus, theophylline, thyroxine, tocainide, tricyclic anti-depressants, voriconazole, warfarin, and zidovudine. To maintain optimum therapeutic effect of these drugs, clinicians may have to adjust the dosage when rifampin is started or stopped. Conversely, protease inhibitors, as well as other drugs (eg, azoles, the macrolide clarithromycin, nonnucleoside reverse transcriptase inhibitors) inhibit CYP450 enzymes and increase levels of rifamycins and thus potentially increase the frequency of toxic reactions. For example, uveitis occurs more commonly when rifabutin is used with clarithromycin or azoles.

Rifaximin

Rifaximin is a derivative of rifamycin that is poorly absorbed after oral administration; 97% is recovered primarily unchanged in feces. Rifaximin can be used for empiric treatment of traveler's diarrhea, which is caused primarily by enterotoxigenic and enteroaggregative *Escherichia coli*. Rifaximin is not known to be

effective for diarrhea due to enteric pathogens other than *E. coli*. Because rifaximin is not systemically absorbed, it should not be used to treat infectious diarrhea caused by invasive enteric bacterial pathogens (eg, salmonellae, *Campylobacter* sp).

The dose is 200 mg q 8 h for 3 days in adults and children > 12 yr.

Adverse effects include nausea, vomiting, abdominal pain, and flatulence.

Sulfonamides

Sulfonamides (see Table 132-18) are synthetic bacteriostatic antibiotics that competitively inhibit conversion of *p*-aminobenzoic acid to dihydropteroate, which bacteria need for folate synthesis and ultimately purine and DNA synthesis. Humans do not synthesize folate but acquire it in their diet, so their DNA synthesis is less affected.

Two sulfonamides, sulfisoxazole and sulfamethizole, are available as single drugs for oral use. Sulfamethoxazole may be combined with trimethoprim (TMP/SMX—see p. 1221). Sulfadoxine plus pyrimethamine is available (but not in the US) as an oral, fixed combination for malaria due to chloroquine-resistant *Plasmodium falciparum*.

Sulfonamides available for topical use include silver sulfadiazine, vaginal cream and suppositories containing sulfanilamide, and ophthalmic sulfacetamide.

Pharmacology

Most sulfonamides are readily absorbed orally and, when applied to burns, topically. Sulfonamides are distributed throughout the body. They are metabolized mainly by the liver and excreted by the kidneys. Sulfonamides compete for bilirubin-binding sites on albumin.

[**Table 132-18.** Sulfonamides]

Indications

Sulfonamides are active against

• A broad spectrum of gram-positive and many gram-negative bacteria

• *Plasmodium* and *Toxoplasma* spp

However, resistance is widespread, and resistance to one sulfonamide indicates resistance to all.

Sulfasalazine can be used orally for inflammatory bowel disease. Sulfonamides are most commonly used with other drugs (eg, for nocardiosis, UTI, and chloroquine-resistant falciparum malaria).

Topical sulfonamides can be used to treat the following:

• Burns: Silver sulfadiazine and mafenide acetate

• Vaginitis: Vaginal cream and suppositories with sulfanilamide

• Superficial ocular infections: Ophthalmic sulfacetamide

Contraindications

Sulfonamides are contraindicated in patients who have had an allergic reaction to them or who have porphyria. Sulfonamides do not eradicate group A streptococci in patients with pharyngitis and should not be used to treat group A streptococcal pharyngitis.

Use During Pregnancy and Breastfeeding

Most sulfonamides are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). However, use near term and in breastfeeding mothers is contraindicated, as is use in patients < 2 mo (except as adjunctive therapy with pyrimethamine to treat congenital toxoplasmosis). If used during pregnancy or in neonates, these drugs increase blood levels of unconjugated bilirubin and increase risk of kernicterus in the fetus or neonate.

Sulfonamides enter breast milk.

Adverse Effects

Adverse effects can result from oral and sometimes topical sulfonamides; effects include

• Hypersensitivity reactions, such as rashes, Stevens-Johnson syndrome (see p.), vasculitis, serum sickness, drug fever, anaphylaxis, and angioedema

• Crystalluria, oliguria, and anuria

• Hematologic reactions, such as agranulocytosis, thrombocytopenia, and, in patients with G6PD deficiency, hemolytic anemia

• Kernicterus in neonates

• Photosensitivity

• Neurologic effects, such as insomnia, and headache

Hypothyroidism, hepatitis, and activation of quiescent SLE may occur in patients taking sulfonamides. These drugs can exacerbate porphyrias.

Incidence of adverse effects is different for the various sulfonamides, but cross-sensitivity is common.

Sulfasalazine can reduce intestinal absorption of folate (folic acid). Thus, use of this drug may trigger folate deficiency in patients with inflammatory bowel disease, which also reduces absorption, especially if dietary intake is also inadequate.

Mafenide may cause metabolic acidosis by inhibiting carbonic anhydrase.

Dosing Considerations

To avoid crystalluria, clinicians should hydrate patients well (eg, to produce a urinary output of 1200 to 1500 mL/day). Sulfonamides can be used in patients with renal insufficiency, but peak plasma levels should be measured and sulfamethoxazole levels should not exceed 120 μg/mL. Sulfonamides can potentiate sulfonylureas (with consequent hypoglycemia), phenytoin (with increased adverse effects), and coumarin anticoagulants.

Trimethoprim and Sulfamethoxazole

Trimethoprim is available as a single drug or in combination with sulfamethoxazole. The drugs act synergistically to block sequential steps in bacterial folate metabolism. Trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate, and sulfamethoxazole inhibits conversion of *p*-aminobenzoic acid to dihydropteroate. This synergy results in maximal antibacterial activity, which is often bactericidal.

Trimethoprim/sulfamethoxazole (TMP/SMX) is available as a fixed combination consisting of a 1:5 ratio (80 mg TMP plus 400 mg SMX or a double-strength tablet of 160 mg TMP plus 800 mg SMX).

Pharmacology

Both drugs are well absorbed orally and are excreted in the urine. They have a serum half-life of about 11 h in plasma and penetrate well into tissues and body fluids, including CSF. TMP is concentrated in prostatic tissue.

Indications

TMP and TMP/SMX are active against (see
Table 132-19)

• A broad spectrum of gram-positive bacteria (including some methicillin-resistant *Staphylococcus aureus*)

• A broad spectrum of gram-negative bacteria

The combination is inactive against anaerobes, *Treponema pallidum, Mycobacterium tuberculosis, Mycoplasma* sp, and *Pseudomonas aeruginosa*. Enterococci, many Enterobacteriaceae, and *Streptococcus pneumoniae* strains are resistant. TMP/SMX is not clinically effective for group A streptococcal pharyngitis.

[**Table 132-19.** Some Indications for TMP/SMX]

TMP alone is especially useful for chronic bacterial prostatitis and for prophylaxis and treatment of UTI in patients allergic to sulfonamides.

Contraindications

TMP/SMX is contraindicated in patients who have had an allergic reaction to either drug. Relative contraindications include folate deficiency, liver dysfunction, and renal insufficiency.

Use During Pregnancy and Breastfeeding

TMP/SMX is in pregnancy category C (animal studies show some risk, evidence in human studies is inadequate, but clinical benefit sometimes outweighs risk). However, use near term is contraindicated; if used during pregnancy or in neonates, TMP/SMX increases blood levels of unconjugated bilirubin and increases risk of kernicterus in the fetus or neonate.

Sulfonamides enter breast milk and use during breastfeeding is usually discouraged.

Adverse Effects

Adverse effects include

• Those associated with sulfonamide

• Folate deficiency

• Hyperkalemia (TMP can decrease renal tubular K excretion, leading to hyperkalemia)

• Renal insufficiency

Renal failure in patients with underlying renal insufficiency is probably secondary to interstitial nephritis or tubular necrosis. Also, TMP competitively inhibits renal tubular creatinine secretion and may cause an artificial increase in serum creatinine, although GFR remains unchanged. Increases in serum creatinine are more likely in patients with preexisting renal insufficiency and especially in those with diabetes mellitus.

Most adverse effects are the same as for sulfonamides. TMP has adverse effects identical to those of

SMX, but they are less common. Nausea, vomiting, and rash occur most often. AIDS patients have a high incidence of adverse effects, especially fever, rash, and neutropenia.

Folate deficiency (resulting in macrocytic anemia) can also occur. Use of folinic acid can prevent or treat macrocytic anemia, leukopenia, and thrombocytopenia, which sometimes occur with prolonged TMP/SMX use.

Rarely, severe hepatic necrosis occurs. The drug may also cause a syndrome resembling aseptic meningitis.

Dosing Considerations

TMP/SMX may increase warfarin activity and levels of phenytoin, methotrexate, and rifampin. SMX can increase the hypoglycemic effects of sulfonylureas.

Tetracyclines

Tetracyclines (see
Table 132-20) are bacteriostatic antibiotics that bind to the 30S subunit of the ribosome, thus inhibiting bacterial protein synthesis.

Pharmacology

About 60 to 80% of tetracycline and ≥ 90% of doxycycline and minocycline are absorbed after oral use. However, absorption is decreased by metallic cations (eg, aluminum, Ca, Mg, iron); thus, tetracyclines cannot be taken with preparations containing these substances (eg, antacids, many vitamin and mineral supplements). Food decreases absorption of tetracycline but not of doxycycline or minocycline.

Tetracyclines penetrate into most body tissues and fluids. All are concentrated in unobstructed bile. However, CSF levels are not reliably therapeutic. Minocycline is the only tetracycline that reaches high concentrations in tears and saliva. Tetracycline and minocycline are excreted primarily in urine. Doxycycline is excreted primarily in the intestinal tract.

Indications

Tetracyclines are effective against infections caused by the following:

• Rickettsiae

• Spirochetes (eg, *Treponema pallidum, Borrelia burgdorferi*)

• *Helicobacter pylori*

• *Vibrio* sp

• *Yersinia pestis*

• *Francisella tularensis*

• *Brucella* sp

• *Bacillus anthracis*

• *Plasmodium vivax*

• *Plasmodium falciparum*

• *Mycoplasma* sp

• *Chlamydia* and *Chlamydophila* sp

• Some methicillin-resistant *Staphylococcus aureus*

About 5 to 10% of pneumococcal strains and many group A β-hemolytic streptococci, many gram-negative bacillary uropathogens, and penicillinase-producing gonococci are resistant.

[**Table 132-20.** Tetracyclines]

Tetracyclines are interchangeable for most indications, although minocycline has been most studied for methicillin-resistant *S. aureus* infections. Doxycycline is usually preferred for all of the following because it is better tolerated and can be given twice/day:

• Infections caused by rickettsiae and *Chlamydia, Chlamydophila, Mycoplasma*, and *Vibrio* spp

• Acute exacerbations of chronic bronchitis

• Lyme disease

• Brucellosis

• Anthrax

• Plague

• Tularemia

• Granuloma inguinale

• Syphilis

• Prophylaxis of malaria caused by chloroquine-resistant *P. falciparum*

Because of its high concentration in tears and saliva, minocycline is the only tetracycline that can eradicate meningococci in carriers and is an alternate to rifampin for this indication.

Contraindications

Tetracyclines are contraindicated in patients who have had an allergic reaction to them, patients with renal insufficiency (except for doxycycline, which has no dosage adjustment for renal insufficiency), and children ≤ 8 yr (except sometimes for inhalational anthrax).

Use During Pregnancy and Breastfeeding

Tetracyclines are in pregnancy category D (there is evidence of human risk, but clinical benefits may outweigh risk). Tetracyclines cross the placenta, enter fetal circulation, accumulate in fetal bones, and, if used during the 2nd or 3rd trimester, may cause permanent discoloration of teeth. Hepatotoxicity may occur in pregnant women, particularly after IV administration and in those with azotemia or pyelonephritis. Taking high doses during pregnancy can lead to fatty degeneration of the liver, which may be fatal.

Tetracyclines enter breast milk, but usually in small amounts (particularly tetracycline). Use during breastfeeding is usually discouraged.

Adverse Effects

Adverse effects include

• GI disturbances

• *Clostridium difficile*-induced diarrhea (pseudomembranous colitis)

• Candidiasis

• Photosensitivity

• Bone and dental effects in children

• Fatty liver

• Vestibular dysfunction (with minocycline)

All oral tetracyclines cause nausea, vomiting, and diarrhea and can cause *C. difficile*-induced diarrhea (pseudomembranous colitis) and candidal superinfections. If not swallowed with water, tetracyclines can cause esophageal erosions. Photosensitivity due to tetracyclines may manifest as an exaggerated sunburn reaction. Bone and dental effects include staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in children ≤ 8 yr and in fetuses. In infants, tetracyclines may cause idiopathic intracranial hypertension and bulging fontanelles.

Excessive blood levels due to use of high doses or renal insufficiency may lead to fatal acute fatty degeneration of the liver, especially during pregnancy.

Minocycline commonly causes vestibular dysfunction, particularly in women, limiting its use. Use of minocycline has been associated with development of autoimmune disorders such as SLE and polyarteritis nodosa, which may be reversible.

Tetracycline can exacerbate azotemia in patients with renal insufficiency. Expired tetracycline pills can degenerate and, if ingested, cause Fanconi syndrome. Patients should be instructed to discard the drugs when they expire.

Dosing Considerations

Doxycycline, excreted primarily in the intestinal tract, requires no dose reduction in renal insufficiency.

Tetracyclines may decrease the effectiveness of oral contraceptives and potentiate the effects of oral anticoagulants.

Tigecycline

Tigecycline, a derivative of the tetracycline minocycline, is the first available glycylcycline. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. It is bacteriostatic.

Tigecycline is given IV. Tigecycline has a large volume of distribution (> 12 L/kg), penetrating well into bone, lung, liver, and kidney tissues. A half-life of 36 h should provide for once/day dosing. Most of the drug is excreted in bile and feces.

Indications

Tigecycline is effective against many resistant bacteria, including those with resistance to tetracyclines. Tigecycline is active against

• Many gram-positive bacteria, including methicillin-susceptible and methicillin-resistant *Staphylococcus aureus, Streptococcus pneumoniae* with reduced penicillin sensitivity, vancomycin-sensitive *Enterococcus faecalis*, vancomycin-resistant *E. faecium*, and *Listeria* sp

• Many gram-negative bacteria, such as multidrug-resistant *Acinetobacter baumannii, Stenotrophomonas*

maltophilia, Haemophilus influenzae, and most Enterobacteriaceae (including some strains that produce extended-spectrum β-lactamases [ESBLs] and other strains that were carbapenem-resistant based on production of a carbapenemase or metallo-β-lactamase)

• Many atypical respiratory pathogens (chlamydiae, *Mycoplasma* sp), *Mycobacterium abscessus, M. fortuitum,* and anaerobes, including *Bacteroides fragilis, Clostridium perfringens*, and *C. difficile*

It is not effective against *Pseudomonas aeruginosa*, *Providencia* sp, *Morganella morganii*, or *Proteus* sp.

Tigecycline is indicated for complicated skin and soft-tissue infections and complicated intra-abdominal infections, but the drug shows promise for other infections as well. Clinically, tigecycline is used mainly for the following:

• Complicated intra-abdominal infections, including abscesses, appendicitis, cholecystitis, diverticulitis, perforations, and peritonitis

• Complicated skin and soft-tissue infections, including abscesses and infected burns or ulcers

• Community-acquired bacterial pneumonia caused by *S. pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *H. influenzae* (β-lactamase negative isolates), and *Legionella pneumophila*

• Ventilator-associated hospital-acquired pneumonia due to multidrug resistant pathogens

Contraindications

Tigecycline is contraindicated in patients who have had an allergic reaction to it and in children ≤ 8 yr.

Use During Pregnancy and Breastfeeding

Tigecycline is in pregnancy category D (there is evidence of human risk, but clinical benefits may outweigh risk); it, like tetracyclines, can affect fetal bones and teeth.

Whether tigecycline enters breast milk and is safe to use during breastfeeding is unknown.

Adverse Effects

Adverse effects include

• Nausea, vomiting, and diarrhea

• Photosensitivity

• Hepatotoxicity

Nausea and vomiting are common. Increases in serum amylase, total bilirubin concentration, PT, and transaminases can occur in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Many of tigecycline's adverse effects are similar to those of tetracyclines (eg, photosensitivity).

Dosing Considerations

Dose is adjusted in patients with hepatic dysfunction but not in those with renal dysfunction. Serum levels of warfarin may increase, but INR does not appear to increase.

Vancomycin

Vancomycin is a time-dependent bactericidal antibiotic that inhibits cell wall synthesis.

Pharmacology

Vancomycin is not appreciably absorbed from a normal GI tract after oral administration. Given parenterally, it penetrates into bile and pleural, pericardial, synovial, and ascitic fluids. However, penetration into even inflamed CSF is low and erratic. Vancomycin is excreted unchanged by glomerular filtration.

Indications

Vancomycin is active against

• Most gram-positive cocci and bacilli, including almost all *Staphylococcus aureus* and coagulase-negative staphylococcal strains that are resistant to penicillins and cephalosporins

• Many strains of enterococci (via a bacteriostatic mechanism)

However, many strains of enterococci and some strains of *S. aureus* are resistant.

Vancomycin is the drug of choice for serious infection and endocarditis caused by the following:

• Methicillin-resistant *S. aureus*

• Methicillin-resistant coagulase-negative staphylococci

• *Streptococcus pneumoniae*

• β-Hemolytic streptococci (when β-lactams cannot be used because of drug allergy or resistance)

• *Corynebacterium* group JK

• Viridans streptococci (when β-lactams cannot be used because of drug allergy or resistance)

• Enterococci, (when β-lactams cannot be used because of drug allergy or resistance)

However, vancomycin is less effective than antistaphylococcal β-lactams for *S. aureus* endocarditis. Vancomycin is used with other antibiotics when treating methicillin-resistant coagulase-negative staphylococcal prosthetic valve endocarditis or enterococcal endocarditis. Vancomycin has also been used as an alternative drug for pneumococcal meningitis caused by strains with reduced penicillin sensitivity; however, the erratic penetration of vancomycin into CSF (especially during concomitant use of dexamethasone) and reports of clinical failures make it less than optimal when used alone to treat pneumococcal meningitis. Before dental procedures likely to result in bacteremia are done, vancomycin is used to prevent endocarditis in penicillin-allergic high-risk patients who cannot tolerate oral antibiotics.

Oral vancomycin is used to treat *Clostridium difficile*-induced diarrhea (pseudomembranous colitis) only if patients do not respond to metronidazole.

Contraindications

Vancomycin is contraindicated in patients who have had an allergic reaction to it.

Use During Pregnancy and Breastfeeding

Vancomycin has not had adverse effects in animals, and evidence in human studies is inadequate. Oral vancomycin tablets are in pregnancy category B (animal studies show no risk and human evidence is incomplete, or animal studies show risk but human studies do not). Oral-solution vancomycin and IV vancomycin are in category C (animal studies show some risk, evidence in human and animal studies is inadequate, but clinical benefit sometimes exceeds risk).

Vancomycin enters breast milk, and so its use during breastfeeding is discouraged; however, because oral absorption is poor from a normal GI tract, adverse effects in infants are usually considered unlikely.

Adverse Effects

The main concern is

• Hypersensitivity

Hypersensitivity reactions (eg, rash, fever, reversible neutropenia and thrombocytopenia) may occur, especially when therapy lasts for > 2 wk. Nephrotoxicity is rare unless high doses are used or an aminoglycoside is given concomitantly. Phlebitis occurs uncommonly during IV infusion. Infusion should be given over at least 60 min to avoid the red-person syndrome, a histamine-mediated reaction that can cause pruritus and flushing on the face, neck, and shoulders.

Dose-related ototoxicity is unusual with current formulations.

Dosing Considerations

Doses used for meningitis must be higher than usual. Dose reduction is required in renal insufficiency. In critically ill patients, serum levels should be measured after the 2nd or 3rd dose and kept between 10 and 15 μg/mL (trough levels).

Vancomycin MIC has been increasing in the past decade. *S. aureus* with vancomycin MIC of ≤ 2 μg/mL are considered sensitive; those with vancomycin MIC of 4 to 8 μg/mL are considered intermediate, and those with vancomycin MIC of > 8 μg/mL are considered resistant. However, infections due to *S. aureus* with vancomycin MIC of 2 to 8 μg/mL may respond suboptimally to standard dosing and require higher doses with trough levels between 15 to 20 μg/mL, but this approach may be complicated by increased rates of nephrotoxicity.

Chapter 133. Gram-Positive Cocci

Introduction

Many gram-positive cocci are commensal organisms that cause infection only when they find their way into normally sterile areas. They are the most common cause of skin infections and a frequent cause of pneumonia and septicemia. Although they are generally susceptible to a broad range of antibiotics, certain strains have developed resistance to many available antimicrobial drugs.

Pneumococcal Infections

***Streptococcus pneumoniae* (pneumococci) are gram-positive, α-hemolytic, aerobic, encapsulated diplococci. In the US, pneumococcal infection annually causes about 7 million cases of otitis media, 500,000 cases of pneumonia, 50,000 cases of sepsis, 3,000 cases of meningitis, and 40,000 deaths. Diagnosis is by Gram stain and culture. Treatment depends on the resistance profile and includes a β-lactam, a macrolide, a respiratory fluoroquinolone, and sometimes vancomycin.**

Pneumococci are fastidious microorganisms that require catalase to grow on agar plates. In the laboratory, pneumococci are identified by α-hemolysis on blood agar, sensitivity to optochin, and lysis by bile salts.

Pneumococci commonly colonize the human respiratory tract, particularly in winter and early spring. Spread is via airborne droplets. True epidemics of pneumococcal infections are rare.

Serotypes: The pneumococcus capsule consists of a complex polysaccharide that determines serologic type and contributes to virulence and pathogenicity. Virulence varies somewhat within serologic types because of differences in DNA composition.

Currently, > 90 different serotypes have been identified, but most serious infections are caused by serotypes 4, 6, 9, 14, 18, 19, and 23. These serotypes cause about 90% of invasive infections in children and 60% in adults. However, these patterns are slowly changing, in part because of the widespread use of polyvalent vaccine. Serotype 19A, a nonvaccine serotype that is highly virulent and multi-drug-resistant, has emerged as an important cause of respiratory tract infection and invasive disease.

Risk factors: Patients most susceptible to serious and invasive pneumococcal infections are those with chronic illness (eg, chronic cardiorespiratory disease, diabetes, liver disease, alcoholism), immunosuppression (eg, HIV), functional or anatomic asplenia, or sickle cell disease, as well as residents of long-term care facilities, smokers, aborigines, Alaskan natives, and certain American Indian populations. The elderly, even those without other disease, tend to have a poor prognosis with pneumococcal infections. Damage to the respiratory epithelium by chronic bronchitis or common respiratory viral infections, notably influenza, may predispose to pneumococcal invasion.

Diseases Caused by Pneumococci

Pneumococcal diseases include

• Otitis media

• Pneumonia

• Sinusitis

• Meningitis

• Endocarditis

• Septic arthritis

• Peritonitis (rare)

Primary infection usually involves the middle ear or lungs. The diseases listed below are further discussed elsewhere in THE MANUAL.

Pneumococcal bacteremia can occur in immunocompetent and immunosuppressed patients; patients who have had splenectomy are at particular risk. Bacteremia may be the primary infection, or it may accompany the acute phase of any focal pneumococcal infection. When bacteremia is present, secondary seeding of distant sites may cause infections such as septic arthritis, meningitis, and endocarditis. Despite treatment, the overall mortality rate for bacteremia is 15 to 20% in children and adults and 30 to 40% in the elderly; risk of death is highest during the first 72 h.

Pneumonia (see p.) is the most frequent serious infection caused by pneumococci; it may manifest as lobar pneumonia or, less commonly, as bronchopneumonia. About 4 million cases of community-acquired pneumonia occur each year in the US; when community-acquired pneumonia requires hospitalization, pneumococci are the most common etiologic agent in patients of all ages. Pleural effusion occurs in up to 40% of patients, but most effusions resolve during drug treatment; only about 2% of patients develop empyema, which may become loculated, thick, and fibrinopurulent. Lung abscess formation is rare.

Acute otitis media in infants (after the neonatal period) and children is caused by pneumococci in about 30 to 40% of cases (see p.). More than one third of children in most populations develop acute pneumococcal otitis media during the first 2 yr of life, and pneumococcal otitis commonly recurs. Relatively few serotypes of *S. pneumoniae* are responsible for most cases. After universal immunization of infants in the US beginning in 2000, nonvaccine serotypes of *S. pneumoniae* (particularly serotype 19A) have become the most common pneumococcal cause of acute otitis media. Complications include mild conductive hearing loss, vestibular balance dysfunction, tympanic membrane perforation, mastoiditis, petrositis, and labyrinthitis. Intracranial complications are rare in developed countries but may include meningitis, epidural abscess, brain abscess, lateral venous sinus thrombosis, cavernous sinus thrombosis, subdural empyema, and carotid artery thrombosis.

Paranasal sinusitis (see p.) may be caused by pneumococci and may become chronic and polymicrobic. Most commonly, the maxillary and ethmoid sinuses are affected. Infection of the sinuses may extend into the cranium, causing cavernous sinus thrombosis; brain, epidural, or subdural abscesses; septic cortical thrombophlebitis; or meningitis.

Acute purulent meningitis (see p.) is frequently caused by pneumococci and may be secondary to bacteremia from other foci (notably pneumonia); direct extension from infection of the ear, mastoid process, or paranasal sinuses; or basilar fracture of the skull involving one of these sites or the cribriform plate. Complications after pneumococcal meningitis include hearing loss (in up to 50% of patients), seizures, learning disabilities, mental dysfunction, and palsies.

Endocarditis (see p.) may result from pneumococcal bacteremia, even in patients without valvular heart disease, but is rare. Pneumococcal endocarditis may produce a corrosive valvular lesion, with sudden rupture or fenestration, leading to rapidly progressive heart failure.

Septic arthritis, similar to septic arthritis caused by other gram-positive cocci, is usually a complication of pneumococcal bacteremia from another site (see Acute Infectious Arthritis on p.).

Spontaneous pneumococcal peritonitis occurs most often in patients with cirrhosis and ascites, with no features to distinguish it from spontaneous bacterial peritonitis of other causes (see p.).

Diagnosis

• Gram stain and culture

Pneumococci are readily identified by their typical appearance on Gram stain as lancet-shaped diplococci. The characteristic capsule can be best detected using the Quellung test. In this test, application of antiserum followed by staining with India ink causes the capsule to appear like a halo around the organism. The capsule is also visible in smears stained with methylene blue. Culture confirms identification; antimicrobial susceptibility testing should be done. Serotyping and genotyping of isolates can be helpful for epidemiologic reasons (eg, to follow the spread of specific clones and antimicrobial resistance patterns).

Treatment

• A β-lactam or macrolide

If pneumococcal infection is suspected, initial therapy pending susceptibility studies should be determined by local resistance patterns. Although preferred treatment for pneumococcal infections is a β-lactam or macrolide antibiotic, treatment has become more challenging because resistant strains have emerged. Strains highly resistant to penicillin, ampicillin, and other β-lactams are common worldwide. The most common predisposing factor to β-lactam resistance is use of these drugs within the past several months.

Intermediately resistant organisms may be treated with usual or high doses of penicillin G or another β-lactam.

Seriously ill patients with nonmeningeal infections caused by organisms that are highly resistant to penicillin can often be treated with ceftriaxone or cefotaxime. Very high doses of parenteral penicillin G (20 to 40 million units/day IV for adults) also work, unless the minimum inhibitory concentration of the isolate is very high. Fluoroquinolones (eg, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin) are effective for respiratory infections with highly penicillin-resistant pneumococci in adults.

All penicillin-resistant isolates have been susceptible to vancomycin so far, but parenteral vancomycin does not always produce concentrations in CSF adequate for treatment of meningitis (especially if corticosteroids are also being used). Therefore, in patients with meningitis, ceftriaxone or cefotaxime, rifampin, or both are commonly used with vancomycin.

Prevention

Infection produces type-specific immunity that does not generalize to other serotypes. Otherwise, prevention involves

• Vaccination

• Prophylactic antibiotics

Vaccines: Two pneumococcal vaccines are available: a conjugated vaccine against 7 serotypes (PCV7) and a polyvalent polysaccharide vaccine directed against the 23 serotypes (PPV23) that account for 80 to 95% of serious pneumococcal infections.

Conjugated vaccine is recommended for all children aged 6 wk through 59 mo. The schedule varies depending on age and underlying medical conditions (see
Table 268-10 on p. 2718). If vaccination is begun at age ≤ 6 mo, children should receive a 3-dose primary series at about 2-mo intervals, followed by a 4th dose at age 12 to 15 mo. The customary age for the first dose is 2 mo. If vaccination is begun at age 7 to 11 mo, a 2-dose primary series and a booster are given. From age 12 to 23 mo, 2 doses and no booster are given. From age 24 mo to 9 yr, children receive 1 dose.

Polysaccharide vaccine is ineffective in children < 2 yr but reduces pneumococcal bacteremia by 50% in adults. There is no documented reduction in pneumonia. Protection generally lasts many years, but revaccination after ≥ 5 yr may be desirable in highly susceptible people. The polysaccharide vaccine is indicated for adults ≥ 65 yr and people 2 to 64 yr with increased susceptibility (see p. 1226) and before splenectomy. It is not recommended for children < 2 yr or anyone hypersensitive to the vaccine's

components.

Prophylactic antibiotics: For functional or anatomic asplenic children < 5 yr, penicillin V 125 mg po bid is recommended. The duration for chemoprophylaxis is empiric, but some experts continue prophylaxis throughout childhood and into adulthood for high-risk patients with asplenia. Penicillin 250 mg po bid is recommended for older children or adolescents for at least 1 yr after splenectomy.

Staphylococcal Infections

Staphylococci are gram-positive, aerobic organisms. *Staphylococcus aureus* is the most pathogenic; it typically causes skin infections and sometimes pneumonia, endocarditis, and osteomyelitis. It commonly leads to abscess formation. Some strains elaborate toxins that cause gastroenteritis, scalded skin syndrome, and toxic shock syndrome. Diagnosis is by Gram stain and culture. Treatment is usually with penicillinase-resistant b-lactams, but because antibiotic resistance is common, vancomycin or other newer antibiotics may be required. Some strains are partially or totally resistant to all but the newest antibiotics, which include linezolid, quinupristin/dalfopristin, daptomycin, telavancin, dalbavancin, and tigecycline.

The ability to clot blood by producing coagulase determines the virulence of the several species of staphylococci. Coagulase-positive *Staphylococcus aureus* is among the most ubiquitous and dangerous human pathogens, for both its virulence and its ability to develop antibiotic resistance. Coagulase-negative species such as *S. epidermidis* are increasingly associated with hospital-acquired infections; *S. saprophyticus* causes urinary infections. *S. lugdunensis*, a coagulase-negative species, has recently been found to cause invasive disease with virulence similar to that of *S. aureus*. Unlike most coagulase-negative staphylococcal species, *S. lugdunensis*, often remains sensitive to penicillinase-resistant β-lactam antibiotics.

Pathogenic staphylococci are ubiquitous. They are carried, usually transiently, in the anterior nares of about 30% of healthy adults and on the skin of about 20%. Rates are higher in hospital patients and personnel.

Risk factors: Neonates and breastfeeding mothers are predisposed to staphylococcal infections, as are patients with influenza, chronic bronchopulmonary disorders (eg, cystic fibrosis, emphysema), leukemia, tumors, transplants, implanted prostheses or other foreign bodies, burns, chronic skin disorders, surgical incisions, diabetes mellitus, or indwelling intravascular plastic catheters. Patients receiving adrenal steroids, irradiation, immunosuppressants, or antitumor chemotherapy are also at increased risk. Predisposed patients may acquire antibiotic-resistant staphylococci from other patients, health care personnel, or inanimate objects in health care settings. Transmission via the hands of personnel is the most common means of spread, but airborne spread can also occur.

Diseases Caused by Staphylococci

Staphylococci cause disease by

• Direct tissue invasion

• Sometimes exotoxin production

S. aureus **bacteremia**, which frequently causes metastatic foci of infection, may occur with any localized staphylococcal infection but is particularly common with infection related to intravascular catheters or other foreign bodies. It may also occur without any obvious primary site. *S. epidermidis* and other coagulase-negative staphylococci increasingly cause hospital-acquired bacteremia associated with intravascular catheters and other foreign bodies because they can form biofilms on these materials. They are important causes of morbidity (especially prolongation of hospitalization) and mortality in debilitated patients. The diseases listed below are further discussed elsewhere in THE MANUAL.

Direct invasion: Most staphylococcal disease results from direct tissue invasion. Examples are

• Skin infections

• Pneumonia

• Endocarditis

• Osteomyelitis

• Septic arthritis

Skin infections are the most common form of staphylococcal disease (see p. 694). Superficial infections may be diffuse, with vesicular pustules and crusting (impetigo) or sometimes cellulitis or with focal and nodular abscesses (furuncles and carbuncles). Deeper cutaneous abscesses are common. Severe necrotizing skin infections may occur. Staphylococci are commonly implicated in wound and burn infections, postoperative incision infections, and mastitis or breast abscess in breastfeeding mothers.

Neonatal infections usually appear within 6 wk after birth and include skin lesions with or without exfoliation, bacteremia, meningitis, and pneumonia.

Pneumonia that occurs in a community setting is not common but may develop in patients who have influenza, who are receiving corticosteroids or immunosuppressants, or who have chronic bronchopulmonary or other high-risk diseases. However, *S. aureus* is a common cause of hospital-acquired pneumonia. Staphylococcal pneumonia is occasionally characterized by formation of lung abscesses followed by rapid development of pneumatoceles and empyema. Community-associated methicillin-resistant *S. aureus* (CA-MRSA) often causes severe necrotizing pneumonia.

Endocarditis can develop, particularly in IV drug abusers and patients with prosthetic heart valves. Because intravascular catheter use and implantation of cardiac devices have increased, *S. aureus* has become a leading cause of bacterial endocarditis. *S. aureus* endocarditis is an acute febrile illness often accompanied by visceral abscesses, embolic phenomena, pericarditis, subungual petechiae, subconjunctival hemorrhage, purpuric lesions, heart murmurs, and heart failure secondary to cardiac valve damage.

Osteomyelitis occurs more commonly in children, causing chills, fever, and pain over the involved bone. Redness and swelling subsequently appear. Articular infection may occur; it frequently results in effusion, suggesting septic arthritis rather than osteomyelitis.

Toxin-mediated disease: Staphylococci may produce multiple toxins. Some have local effects; others trigger cytokine release from certain T cells, causing serious systemic effects (eg, skin lesions, shock, organ failure, death). Panton-Valentine leukocidin (PVL) is a toxin produced by strains infected with a certain bacteriophage. PVL is typically present in strains of CA-MRSA and has been thought to mediate the ability to necrotize; however, this effect has not been verified.

Toxin-mediated staphylococcal diseases include the following:

• Toxic shock syndrome

• Staphylococcal scalded skin syndrome

• Staphylococcal food poisoning

Toxic shock syndrome (see p. 1235) may result from use of vaginal tampons or occur as a complication of a seemingly minor postoperative infection. Although most cases have been due to methicillin-susceptible *S. aureus* (MSSA), cases due to MRSA are becoming more frequent.

Staphylococcal scalded skin syndrome (see p. 701 and Plate 45), which is caused by several toxins termed exfoliatins, is an exfoliative dermatitis of childhood characterized by large bullae and peeling of the upper layer of skin. Eventually, exfoliation occurs.

Staphylococcal food poisoning is caused by ingesting a preformed heat-stable staphylococcal enterotoxin. Food can be contaminated by staphylococcal carriers or people with active skin infections. In food that is incompletely cooked or left at room temperature, staphylococci reproduce and elaborate enterotoxin. Many foods can serve as growth media, and despite contamination, they have a normal taste and odor. Severe nausea and vomiting begin 2 to 8 h after ingestion, typically followed by abdominal cramps and diarrhea. The attack is brief, often lasting < 12 h.

Diagnosis

• Gram stain and culture

Diagnosis is by Gram stain and culture of infected material. Susceptibility tests should be done because methicillin-resistant organisms are now common and require alternative therapy.

When staphylococcal scalded skin syndrome is suspected, cultures should be obtained from blood, urine, the nasopharynx, the umbilicus, abnormal skin, or any suspected focus of infection; the intact bullae are sterile. Although the diagnosis is usually clinical, a biopsy of the affected skin may help confirm the diagnosis.

Staphylococcal food poisoning is usually suspected because of case clustering (eg, within a family, attendees of a social gathering, or customers of a restaurant). Confirmation (typically by the health department) entails isolating staphylococci from suspect food and sometimes testing for enterotoxins.

X-ray changes of osteomyelitis may not be apparent for 10 to 14 days, and bone rarefaction and periosteal reaction may not be detected for even longer. Abnormalities in MRI, CT, or radionuclide bone scans are often apparent earlier. Bone biopsy (open or percutaneous) should be done for pathogen identification and susceptibility testing.

Screening: Some institutions that have a high incidence of MRSA nosocomial infections routinely screen admitted patients for MRSA (active surveillance) by using rapid laboratory techniques to evaluate nasal swab specimens. Some institutions screen only high-risk patients (eg, those who are admitted to the ICU, who have had previous MRSA infection, or who are about to undergo vascular, orthopedic, or cardiac surgeries). Quick identification of MRSA allows carriers to be placed in contact isolation. This practice decreases the spread of MRSA and may decrease the incidence of nosocomial infections with MRSA.

Treatment

• Local measures (eg, debridement, removal of catheters)

• Antibiotics selected based on severity of infection and local resistance patterns

Management includes abscess drainage, debridement of necrotic tissue, removal of foreign bodies (including intravascular catheters), and use of antibiotics. Initial choice and dosage of antibiotics depend on infection site, illness severity, and probability that resistant strains are involved. Thus, it is essential to know local resistance patterns for initial therapy (and ultimately, to know actual drug susceptibility).

Treatment of toxin-medicated staphylococcal disease (the most serious of which is toxic shock syndrome) involves decontamination of the toxin-producing area (exploration of surgical wounds, irrigation, debridement), intensive support (including vasopressors and respiratory assistance), electrolyte balancing, and antimicrobials. In vitro evidence supports a preference for protein synthesis inhibitors (eg, clindamycin 900 mg IV q 8 h) over other classes of antibiotics. IV immune globulin has been beneficial in severe cases.

Antibiotic resistance: Many staphylococcal strains produce penicillinase, an enzyme that inactivates several β-lactam antibiotics; these strains are resistant to penicillin G, ampicillin, and antipseudomonal penicillins. Most community-acquired strains are susceptible to penicillinase-resistant penicillins (eg, methicillin, oxacillin, nafcillin, cloxacillin, dicloxacillin), cephalosporins, carbapenems (eg, imipenem,

meropenem, ertapenem, doripenem), macrolides, fluoroquinolones, trimethoprim/sulfamethoxazole (TMP/SMX), gentamicin, vancomycin, and teicoplanin.

MRSA isolates have become common, especially in hospitals. In addition, CA-MRSA has emerged over the past several years in many geographic regions. CA-MRSA tends to be less resistant to multiple drugs than hospital-acquired MRSA. These strains, although resistant to most β-lactams, are usually susceptible to TMP/SMX, doxycycline, or minocycline and are often susceptible to clindamycin, but there is the potential for emergence of clindamycin resistance by strains inducibly resistant to erythromycin (laboratories may report these strains as D-test positive). Vancomycin is effective against most MRSA, sometimes with the addition of rifampin and an amino-glycoside for serious infections.

Vancomycin-resistant *S. aureus* (VRSA) and vancomycin-intermediate-susceptible *S. aureus* (VISA) strains have appeared in the US. These organisms may require linezolid, quinupristin/dalfopristin, or daptomycin.

Because incidence of MRSA has increased, initial empiric treatment for serious staphylococcal infections (particularly those that occur in a health care setting) should include a drug with reliable activity against MRSA. Thus, for proven or suspected bloodstream infections, vancomycin or daptomycin would be appropriate. For pneumonia, vancomycin or linezolid should be used because daptomycin is not reliably active in the lungs.

Table 133-1 summarizes treatment options.

Prevention

Aseptic precautions (eg, thoroughly washing hands between patient examinations, sterilizing shared equipment) help decrease spread in institutions. Strict isolation procedures should be used for patients harboring resistant microbes until their infections have been cured. An asymptomatic nasal carrier need not be isolated unless the strain is MRSA or is the suspected source of an outbreak. Cloxacillin, dicloxacillin, TMP/SMX, ciprofloxacin (each of these drugs is often combined with rifampin), and topical mupirocin have been useful in treating MRSA in carriers, but the organism recurs in up to 50% and frequently becomes resistant.

Staphylococcal food poisoning can be prevented by appropriate food preparation. Patients with staphylococcal skin infections should not handle food, and food should be consumed immediately or refrigerated and not kept at room temperature.

Streptococcal and Enterococcal Infections

(See also Pneumococcal Infections on p. 1225, Rheumatic Fever on p. 2861, and Tonsillopharyngitis on p. 473.)

Streptococci are gram-positive aerobic organisms that cause many disorders, including pharyngitis, pneumonia, wound and skin infections, sepsis, and endocarditis. Symptoms vary with the organ infected. Sequelae include

[**Table 133-1.** Antibiotic Treatment of Staphylococcal Infections in Adults]

rheumatic fever and glomerulonephritis. Clinical diagnoses are confirmed by Gram stain and culture. Most strains are sensitive to penicillin, with the exception of enterococci, which can be resistant to multiple drugs. Recently, macrolide-resistant strains have emerged.

Classification: Three different types of streptococci are initially differentiated by their appearance when they are grown on sheep blood agar. β-Hemolytic streptococci produce zones of clear hemolysis around each colony, α-hemolytic streptococci (including viridans group streptococci) are surrounded by green discoloration resulting from incomplete hemolysis, and γ-hemolytic streptococci are nonhemolytic.

Subsequent classification, based on carbohydrates in the cell wall, divides streptococci into Lancefield

groups A through H and K through T (see Table 133-2). Viridans streptococci form a separate group that is difficult to classify. In the Lancefield classification, enterococci were initially included among the group D streptococci. More recently, enterococci have been classified as a separate genus.

Virulence factors: Many streptococci elaborate virulence factors, including streptolysins, DNAases, and hyaluronidase, which contribute to tissue destruction and spread of infection. A few strains release exotoxins that activate certain T cells, triggering release of cytokines, including tumor necrosis factor-α, interleukins, and other immunomodulators. These cytokines activate the complement, coagulation, and fibrinolytic systems, leading to shock, organ failure, and death.

Diseases Caused by Streptococci

The most significant streptococcal pathogen is *S. pyogenes*, which is β-hemolytic and in Lancefield group A and is thus denoted as group A β-hemolytic streptococci (GABHS). The 2 most common acute diseases due to GABHS are pharyngitis and skin infections; in addition, delayed, nonsuppurative complications (rheumatic fever, acute glomerulonephritis) sometimes occur ≥ 2 wk after infection.

Disease caused by other streptococcal species is less prevalent and usually involves soft-tissue infection or endocarditis (see Table 133-2). Some non-GABHS infections occur predominantly in certain populations (eg, group B streptococci in neonates and postpartum women, enterococci in hospitalized patients).

Infections can spread through the affected tissues and along lymphatic channels to regional lymph nodes. They can also cause local suppurative complications, such as peritonsillar abscess, otitis media, sinusitis, and

[**Table 133-2.** Classification of Streptococci]

bacteremia. Suppuration depends on the severity of infection and the susceptibility of tissue.

Streptococcal pharyngitis is usually caused by GABHS. About 20% of patients present with sore throat, fever, a beefy red pharynx, and a purulent tonsillar exudate. The remainder have less prominent symptoms, and the examination resembles that of viral pharyngitis. The cervical and submaxillary nodes may enlarge and become tender. Streptococcal pharyngitis can lead to peritonsillar abscess (see p. 474). Cough, laryngitis, and stuffy nose are not characteristic of streptococcal pharyngeal infection; their presence suggests another cause (usually viral or allergic). An asymptomatic carrier state may exist in as many as 20%.

Scarlet fever is uncommon today. Scarlet fever is caused by group A (and occasionally by group B or C) streptococcal strains that produce an erythrogenic toxin, leading to a diffuse pink-red cutaneous flush that blanches with pressure. The rash is seen best on the abdomen or lateral chest as dark red lines in skinfolds (Pastia's lines) or as circumoral pallor. A strawberry tongue (inflamed papillae protruding through a bright red coating) also occurs and must be differentiated from that seen in toxic shock syndrome (see p. 1235) and Kawasaki disease (see p. 2935). Characteristic numerous small (1- to 2-mm) papular elevations, giving a sandpaper quality to the skin, may be present. The upper layer of the previously reddened skin often desquamates after fever subsides. Other symptoms are similar to those in streptococcal pharyngitis, and the course and management of scarlet fever are the same as those of other group A infections.

Skin infections include impetigo (see p. 699) and cellulitis (see p. 694). Cellulitis may spread rapidly because of the numerous lytic enzymes and toxins produced mainly by group A streptococci. Erysipelas (see p. 696) is a particular form of streptococcal cellulitis.

Necrotizing fasciitis due to *S. pyogenes* is a severe dermal (or rarely muscular) infection that spreads along fascial planes (see p. 700). Inoculation originates through the skin or bowel, and the defect may be surgical, trivial, distant from the disease site, or occult, as with colonic diverticula or an appendiceal abscess. Necrotizing fasciitis is prevalent among IV drug abusers. Formerly known as streptococcal

gangrene and popularized as the flesh-eating bacteria, the same syndrome may also be polymicrobial, involving a host of aerobic and anaerobic flora, including *Clostridium perfringens*. When necrotizing fasciitis occurs in the perineum, it is called Fournier's gangrene (see Plate 61). Comorbid conditions, such as impaired immunity, diabetes, and alcoholism, are common. Symptoms begin with fever and exquisite localized pain; pain increases rapidly over time and is often the first (and sometimes only) manifestation. Diffuse or local erythema may be present. Thrombosis of the microvasculature causes ischemic necrosis, leading to rapid spread and disproportionally severe toxicity. In 20 to 40% of patients, adjacent muscles are invaded. Shock and renal dysfunction are common. Mortality is high, even with treatment.

Other serious streptococcal infections include septicemia, puerperal sepsis, endocarditis, and pneumonia.

Streptococcal toxic shock syndrome (see p.), similar to that caused by *S. aureus*, may result from toxin-producing strains of GABHS. Patients are usually otherwise healthy children or adults with skin and soft-tissue infections.

Delayed complications: The mechanism by which certain strains of GABHS cause delayed complications is unclear but may involve cross-reactivity of streptococcal antibodies against host tissue.

Rheumatic fever (see p.), an inflammatory disorder, occurs in < 3% of patients in the weeks after untreated GABHS upper respiratory tract infection. It is much less common today than in the preantibiotic era. Diagnosis is based on a combination of arthritis, carditis, chorea, specific cutaneous manifestations, and laboratory test results (Jones criteria). One of the most important reasons for treating strep throat is to prevent rheumatic fever.

Poststreptococcal acute glomerulonephritis (see p.) is an acute nephritic syndrome following pharyngitis or skin infection due to a certain limited number of nephritogenic strains of GABHS (eg, types 12 and 49). After a throat or skin infection with one of these strains, about 10 to 15% of patients develop acute glomerulonephritis. It is most common among children, occurring 1 to 3 wk after infection. Nearly all children, but somewhat fewer adults, recover without permanent renal damage. Antibiotic treatment of GABHS infection has little effect on development of glomerulonephritis.

PANDAS syndrome (pediatric autoimmune neuropsychiatric disorder associated with group A streptococci) refers to a subset of obsessive disorders or tic disorders in children thought to be exacerbated by GABHS infection.

Certain forms of **psoriasis** (eg, guttate) may also be related to β-hemolytic streptococcal infections.

Diagnosis

• Culture

• Sometimes rapid antigen tests or antibody titers

Streptococci are readily identified by culture on a sheep blood agar plate.

Rapid antigen-detection tests that can detect GABHS directly from throat swabs are available. Many tests use enzyme immunoassay, but more recently, tests using optical immunoassay have become available. These rapid tests have high specificity (> 95%) but vary considerably in sensitivity (55% to 80 to 90% for the newer optical immunoassay test). Negative results should be confirmed by culture (particularly if use of a macrolide is being considered because of potential resistance).

During convalescence, evidence of infection can be obtained indirectly by demonstrating antistreptococcal antibodies in serum. Antibodies are most useful in diagnosis of poststreptococcal diseases, such as rheumatic fever and glomerulonephritis. Confirmation requires that sequential specimens show a rise in titer because a single value may be high because of a long antecedent infection. Serum specimens need not be taken more often than every 2 wk and may be taken every 2 mo. To be considered significant, a rise (or fall) in titer should span at least 2 serial dilutions. The antistreptolysin O (ASO) titer rises in only 75 to 80% of infections. For completeness in difficult cases, any

one of the other tests (antihyaluronidase, antideoxyribonuclease B, antinicotinamide adenine dinucleotidase, antistreptokinase) can also be used. Penicillin given within the first 5 days for symptomatic streptococcal pharyngitis may delay the appearance and decrease the magnitude of the ASO response. Patients with streptococcal pyoderma usually do not have a significant ASO response but may have a response to other antigens (ie, anti-DNAase, antihyaluronidase).

Treatment

• Usually penicillin

Pharyngitis: Ordinarily, pharyngeal GABHS infections, including scarlet fever, are self-limited. Antibiotics shorten the course in young children, especially those with scarlet fever, but have only modest effect on symptoms in adolescents and adults. However, antibiotics help prevent local suppurative complications (eg, peritonsillar abscess), otitis media, and rheumatic fever.

Penicillin is the drug of choice. No isolate of GABHS has demonstrated penicillin resistance clinically, probably because it lacks altered penicillin-binding proteins, has an inefficient gene transfer mechanism for resistance, or both. However, some streptococcal strains appear to have in vitro tolerance to penicillin; the clinical significance of such strains is unclear.

A single injection of benzathine penicillin G, 600,000 units IM for small children (< 27.3 kg) or 1.2 million units IM for adolescents and adults usually suffices. Oral penicillin V may be used if the patient can be trusted to maintain the regimen for the required 10 days; penicillin V 500 mg (250 mg for children < 27 kg) po bid or tid is given. Oral cephalosporins are also effective. Cefdinir, cefpodoxime, and azithromycin can be used for a 5-day course of therapy. Delaying treatment 1 to 2 days until laboratory confirmation increases neither the duration of disease nor the incidence of complications.

When penicillin or a β-lactam is contraindicated, erythromycin 250 mg po qid or clindamycin 300 mg po tid may be given for 10 days, although resistance of GABHS to macrolides has been detected. Some authorities recommend in vitro confirmation of susceptibility if a macrolide is to be used and there is macrolide resistance in the community. Clindamycin 5 mg/kg po qid is preferred in children who have relapses of chronic tonsillitis, possibly because it has good activity against penicillinase-producing staphylococci or anaerobes coinfecting the tonsillar crypts and inactivating penicillin G and because it appears to halt exotoxin production more rapidly than other drugs. Amoxicillin/clavulanate is also effective. TMP/SMX, some of the fluoroquinolones, and tetracyclines are unreliable for treating GABHS.

Sore throat, headache, and fever can be treated with analgesics or antipyretics. Bed rest and isolation are unnecessary. Close contacts who are symptomatic or have a history of poststreptococcal complications should be examined for streptococci.

Skin infection: Cellulitis is often treated without doing a culture because isolating organisms can be difficult. Thus, regimens effective against both streptococci and staphylococci are used (see p.).

Necrotizing fasciitis should be treated in an ICU. Extensive (sometimes repeated) surgical debridement is required. A recommended initial antibiotic regimen is a β-lactam (often a broad-spectrum drug until etiology is confirmed by culture) plus clindamycin. Although streptococci remain susceptible to β-lactam antibiotics, animal studies show that penicillin is not always effective against a large bacterial inoculum because the streptococci are not rapidly growing.

Other streptococcal infections: Drugs of choice for treating group B, C, and G infections are penicillin, ampicillin, or vancomycin. Cephalosporins or macrolides are usually effective, but susceptibility tests must guide therapy, especially in very ill, immunocompromised, or debilitated people and in people with foreign bodies at the infection site. Surgical wound drainage and debridement as adjuncts to antimicrobial therapy may be lifesaving.

S. bovis is relatively susceptible to antibiotics. Although vancomycin-resistant *S. bovis* isolates have been reported, the organism remains susceptible to penicillin and aminoglycosides.

Most viridans streptococci are often susceptible to penicillin G and other β-lactams. Resistance is growing, and therapy for such strains should be dictated by results of in vitro susceptibility tests.

Enterococcal Infections

***Enterococcus faecalis* and *E. faecium* cause endocarditis, UTI, intra-abdominal infection, cellulitis, and wound infection as well as concurrent bacteremia.**

Enterococci associated with endocarditis are difficult to eradicate unless a combination of a cell wall-active drug (eg, penicillin, ampicillin, vancomycin) plus an aminoglycoside (eg, gentamicin, streptomycin) is used.

For complicated skin infections due to vancomycin-susceptible enterococci, daptomycin and tigecycline are effective treatment options. Tigecycline is recommended for complicated intra-abdominal infections.

Resistance: Vancomycin-resistant enterococci (VRE) may exist; they may be resistant to other glycopeptides (eg, teicoplanin), aminoglycosides, and cell wall-active β-lactams (eg, penicillin G, ampicillin). When identified, infected patients are strictly isolated. Recommended treatment includes streptogramins (quinupristin/dalfopristin for *Enterococcus faecium* only) and oxazolidinones (linezolid). Daptomycin and tigecycline have in vitro activity against VRE and may be off-label treatment options.

β-Lactamase-producing enterococci are occasionally encountered. Combination β-lactam/β-lactamase inhibitor antibiotics (eg, piperacillin/tazobactam, ampicillin/sulbactam) or vancomycin can be used.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is caused by staphylococcal or streptococcal exotoxins. Symptoms include high fever, hypotension, diffuse erythematous rash, and multiple organ dysfunction, which may rapidly progress to severe and intractable shock. Diagnosis is made clinically and by isolating the organism. Treatment includes antibiotics, intensive support, and immune globulin.

TSS is caused by exotoxin-producing cocci. Strains of phage-group 1 *Staphylococcus aureus* elaborate the TSS toxin-1 (TSST-1) or related exotoxins; certain strains of *Streptococcus pyogenes* produce at least 2 exotoxins.

Staphylococcal toxic shock: Women who have preexisting staphylococcal colonization of the vagina and who use tampons are at highest risk. Mechanical or chemical factors related to tampon use probably enhance production of the exotoxin or facilitate its entry into the bloodstream through a mucosal break or via the uterus. Estimates made from small series suggest about 3 cases/100,000 menstruating women still occur, and cases are still reported in women who do not use tampons, in women who have had surgery, and in postpartum women. About 15% of cases occur postpartum or as a complication of postoperative staphylococcal wound infections, which frequently appear insignificant. Cases have also been reported in patients with influenza, osteomyelitis, or cellulitis.

Mortality from staphylococcal TSS is < 3%. Recurrences are common among women who continue to use tampons during the first 4 mo after an episode.

Streptococcal toxic shock: The syndrome is similar to that caused by *S. aureus*, but mortality is higher (20 to 60%). In addition, about 50% of patients have *S. pyogenes* bacteremia, and 50% have necrotizing fasciitis (neither is common with staphylococcal TSS). Patients are usually otherwise healthy children or adults. Primary infections in skin and soft tissue are more common than in other sites. In contrast to staphylococcal TSS, streptococcal TSS is more likely to cause acute respiratory distress syndrome (ARDS) and less likely to cause a typical cutaneous reaction.

S. pyogenes TSS is defined as any group A β-hemolytic streptococci (GABHS) infection associated with shock and organ failure. Risk factors for GABHS TSS include minor trauma, surgical procedures, viral infections (eg, varicella), and use of NSAIDs.

Symptoms and Signs

Onset is sudden, with fever (39° to 40.5°C, which remains elevated), hypotension, a diffuse macular erythroderma, and involvement of at least 2 other organ systems.

Staphylococcal TSS is likely to cause vomiting, diarrhea, myalgia, elevated CK, mucositis, hepatic damage, thrombocytopenia, and confusion. The staphylococcal TSS rash is more likely to desquamate, particularly on the palms and soles, between 3 and 7 days after onset.

Streptococcal TSS commonly causes respiratory distress syndrome, coagulopathy, and hepatic damage and is more likely to cause fever, malaise, and severe pain at the site of a soft-tissue infection.

Renal impairment is frequent and common to both. The syndrome may progress within 48 h to syncope, shock, and death. Less severe cases of staphylococcal TSS are fairly common.

Diagnosis

• Clinical evaluation

• Cultures

Diagnosis is made clinically and by isolating the organism from blood cultures (for *Streptococcus*) or from the local site. TSS resembles Kawasaki disease, but Kawasaki disease usually occurs in children < 5 yr of age and does not cause shock, azotemia, or thrombocytopenia; the skin rash is maculopapular. Other disorders to be considered are scarlet fever, Reye's syndrome, staphylococcal scalded skin syndrome, meningococcemia, Rocky Mountain spotted fever, leptospirosis, and viral exanthematous diseases. These disorders are ruled out by specific clinical differences, cultures, and serologic tests.

Specimens for culture should be taken from any lesions, the nose (for staphylococci), throat (for streptococci), vagina (for both), and blood. MRI or CT of soft tissue is helpful in localizing sites of infection. Continuous monitoring of renal, hepatic, bone marrow, and cardiopulmonary function is necessary.

Treatment

• Local measures (eg, decontamination, debridement)

• Fluid resuscitation and circulatory support

• A β-lactam (eg, penicillin) plus clindamycin

Patients suspected of having TSS should be hospitalized immediately and treated intensively. Tampons, diaphragms, and other foreign bodies should be removed at once. Suspected primary sites should be decontaminated thoroughly. Decontamination includes reinspection and irrigation of surgical wounds, even if they appear healthy; repeated debridement of devitalized tissues; and irrigation of potential naturally colonized sites (sinuses, vagina). Fluids and electrolytes are replaced to prevent or treat hypovolemia, hypotension, and shock. Because fluid loss into tissues can occur throughout the body (because of systemic capillary leak syndrome and hypoalbuminemia), shock may be profound and resistant. Aggressive fluid resuscitation and circulatory support are sometimes required.

Obvious infections should be treated. If *S. pyogenes* is isolated, a β-lactam (eg, penicillin) plus clindamycin (900 mg IV q 8 h) continued for 14 days is the most effective antibiotic treatment. If methicillin-resistant *S. aureus* (MRSA—see p.) is suspected or confirmed, vancomycin, daptomycin, linezolid, or tigecycline is indicated. Antibiotics given during the acute illness may eradicate pathogen foci and prevent recurrences. Passive immunization to TSS toxins with IV immune globulin (400 mg/kg) has been helpful in severe cases of both types of TSS and lasts for weeks, but the disease may not induce active immunity, so recurrences are possible.

If a test for seroconversion of the serum antibody responses to TSST-1 in acute- and convalescent-phase paired sera is negative, women who have had staphylococcal TSS should probably refrain from using tampons and cervical caps, plugs, and diaphragms. Advising all women, regardless of TSST-1 antibody status, to change tampons frequently or use napkins instead and to avoid hyperabsorbent tampons seems prudent.

Chapter 134. Gram-Positive Bacilli

Introduction

Gram-positive bacilli cause anthrax, diphtheria, erysipelothricosis, listeriosis, and nocardiosis. Serious symptoms caused by anthrax and diphtheria are due to powerful toxins produced by the organisms.

Anthrax

Anthrax is caused by *Bacillus anthracis*, toxin-producing, encapsulated, aerobic or facultative anaerobic organisms. Anthrax, an often fatal disease of animals, is transmitted to humans by contact with infected animals or their products. In humans, infection typically occurs through the skin. Inhalation infection is less common; oropharyngeal, meningeal, and GI infections are rare. For inhalation and GI infections, nonspecific local symptoms are typically followed in several days by severe systemic illness, shock, and often death. Empiric treatment is with ciprofloxacin or doxycycline. A vaccine is available.

Etiology

Anthrax is an important domestic animal disease, occurring in goats, cattle, sheep, and horses. Anthrax also occurs in wildlife, such as hippos, elephants, and Cape buffalo. It is rare in humans and occurs mainly in countries that do not prevent industrial or agricultural exposure to infected animals or their products (eg, hides). The incidence of natural infection has decreased, particularly in the developed world.

However, the potential use of anthrax as a biological weapon has increased fear of this pathogen. Spores have been prepared in very finely powdered form (weaponized) to be used as agents of warfare and bioterrorism (see p.); in anthrax bioattacks of 2001, spores were spread via the United States Postal Service.

Pathophysiology

Bacillus anthracis readily form spores when they dry—an environmental condition unfavorable for growth. Spores resist destruction and can remain viable in soil, wool, and animal hair for decades. Spores germinate and begin multiplying rapidly when they enter an environment rich in amino acids and glucose (eg, tissue, blood).

Human infection can be acquired by

• Cutaneous contact (most common)

• Ingestion

• Inhalation

Cutaneous infection is usually acquired by contact with infected animals or sporecontaminated animal products. Open wounds or abrasions increase susceptibility, but infection may occur when skin is intact. Skin infection may be transmitted from person to person by direct contact or fomites.

GI (including oropharyngeal) infection may occur after ingestion of inadequately cooked meat containing the vegetative forms of the organism, usually when a break in the pharyngeal or intestinal mucosa facilitates invasion. Ingested anthrax spores can cause lesions from the oral cavity to the cecum. Released toxin causes hemorrhagic necrotic ulcers and mesenteric lymphadenitis, which may lead to intestinal hemorrhage, obstruction, or perforation.

Pulmonary infection (inhalation anthrax), caused by inhaling spores, is almost always due to occupational exposure to contaminated animal products (eg, hides) and is often fatal.

GI and inhalation anthrax are not transmitted from person to person.

After entering the body, spores germinate inside macrophages, which migrate to regional lymph nodes where the bacteria multiply. In inhalation anthrax, spores are deposited in alveolar spaces, where they are ingested by macrophages, which migrate to mediastinal lymph nodes, usually causing a hemorrhagic mediastinitis. Bacteremia may occur in any form of anthrax and occurs in nearly all fatal cases; meningeal involvement is common.

Virulence factors: The virulence of *B. anthracis* is due to its antiphagocytic capsule, its toxins (factors), and its rapid replication capability.

The predominant toxins are edema toxin and lethal toxin. Protective antigen binds to target cells and facilitates cellular entry of edema toxin and lethal toxin. Edema toxin causes massive local edema. Lethal toxin triggers a massive release of cytokines from macrophages, which is responsible for the sudden death common in anthrax infections.

Symptoms and Signs

Most patients present within 1 to 6 days of exposure, but for inhalation anthrax, the incubation period can be > 6 wk.

Cutaneous anthrax begins as a painless, pruritic, red-brown papule 1 to 10 days after exposure to infective spores. The papule enlarges with a surrounding zone of brawny erythema and marked edema (see Plate 58). Vesiculation and induration are present. Central ulceration follows, with serosanguineous exudation and formation of a black eschar (the malignant pustule). Local lymphadenopathy is common, occasionally with malaise, myalgia, headache, fever, nausea, and vomiting. It may take several weeks for the wound to heal and the edema to resolve.

GI anthrax ranges from asymptomatic to fatal. Fever, nausea, vomiting, abdominal pain, and bloody diarrhea are common. Ascites may be present. Intestinal necrosis and septicemia with potentially lethal toxicity ensue.

Oropharyngeal anthrax manifests as edematous lesions with central necrotic ulcers on the tonsils, posterior pharyngeal wall, or hard palate. Soft-tissue swelling in the neck is marked, and cervical lymph nodes are enlarged. Symptoms include hoarseness, sore throat, fever, and dysphagia. Airway obstruction may occur.

Inhalation anthrax begins insidiously as a flu-like illness. Within a few days, fever worsens, and chest pain and severe respiratory distress develop, followed by cyanosis, shock, and coma. Severe hemorrhagic necrotizing lymphadenitis develops and spreads to adjacent mediastinal structures. Serosanguineous transudation, pulmonary edema, and bloody pleural effusion occur. Typical bronchopneumonia does not occur. Hemorrhagic meningoencephalitis or GI anthrax may develop.

Diagnosis

• Gram stain and culture

Occupational and exposure history is important. Cultures and Gram stain of samples from clinically identified sites, including cutaneous or mucosal lesions, pleural fluid, CSF, ascites, or stool, should be done. Sputum examination and Gram stain are unlikely to identify inhalation anthrax because airspace disease is frequently absent. A PCR test and immunohistochemical methods can help. Nasal swab testing for spores in people potentially exposed to inhalation anthrax is not recommended because the predictive value is unknown.

Chest x-ray (or CT) should be done if pulmonary symptoms are present. It typically shows widening of the mediastinum (because of enlarged hemorrhagic lymph nodes) and pleural effusion. Pneumonic infiltrates are uncommon. Lumbar puncture should be done if patients have meningeal signs or a change in mental status. An enzyme-linked immunosorbent assay (ELISA) is available, but confirmation requires a 4-fold

change in antibody titer from acute to convalescent specimens.

Prognosis

Mortality in untreated anthrax varies depending on infection type:

• Inhalation and meningeal anthrax: 100%

• Cutaneous anthrax: 10 to 20%

• GI anthrax: About 50%

• Oropharyngeal anthrax: 12.4 to 50%

Treatment

• Ciprofloxacin or doxycycline

Cutaneous anthrax without significant edema or systemic symptoms is treated with ciprofloxacin 500 mg (10 to 15 mg/kg for children) po q 12 h or doxycycline 100 mg (2.5 mg/kg for children) po q 12 h for 7 to 10 days. Treatment is extended to 60 days if concomitant inhalation exposure was possible. Children and pregnant or breastfeeding women, who typically should not be given ciprofloxacin or doxycycline, should nonetheless be given one of these drugs; however, if prolonged treatment is needed, they may be switched to amoxicillin 500 mg (15 to 30 mg/kg for children) tid after 14 to 21 days if the organism is shown to be susceptible to penicillin. Mortality is rare with treatment, but the lesion will progress through the eschar phase.

Inhalation and other forms of anthrax, including cutaneous anthrax with significant edema or systemic symptoms, require therapy with 2 or 3 drugs: ciprofloxacin 400 mg (10 to 15 mg/kg for children) IV q 12 h or doxycycline 100 mg (2.5 mg/kg for children) IV q 12 h, plus penicillin, ampicillin, imipenem/cilastatin, meropenem, rifampin, vancomycin, clindamycin, or clarithromycin. Corticosteroids may be useful for meningitis and severe mediastinal edema but have not been evaluated adequately. Ca channel blockers, ACE inhibitors, and specific hyperimmune globulin for *B. anthracis* may be considered. With early diagnosis and intensive support, including mechanical ventilation, fluids, and vasopressors, mortality may be reduced to 50%. If treatment is delayed (usually because the diagnosis is missed), death is likely.

Drug resistance is a theoretical concern. Although normally sensitive to penicillin, *B. anthracis* manifests inducible β-lactamases, so single-drug therapy with a penicillin or a cephalosporin is not recommended. Biological warfare researchers may have created strains of anthrax that are resistant to multiple antibiotics, but these strains have not yet been encountered in a clinical situation.

Prevention

An anthrax vaccine, composed of a cellfree culture filtrate, is available for people at high risk (eg, military personnel, veterinarians, laboratory technicians, employees of textile mills processing imported goat hair). A separate veterinary vaccine is also available. Repeated vaccination is required to ensure protection. Local reactions from vaccine can occur.

Limited data suggest that cutaneous anthrax does not result in acquired immunity, particularly if early effective antimicrobial therapy was used. Inhalation anthrax may provide some immunity in patients who survive, but data are very limited.

Postexposure prophylaxis: Postexposure measures include

• Antibiotics

• Vaccination

Asymptomatic people (including pregnant women and children) exposed to inhaled anthrax require prophylaxis with oral ciprofloxacin 500 mg (10 to 15 mg/kg for children) q 12 h or doxycycline 100 mg (2.5 mg/kg for children) q 12 h for 60 days. If the organism has been shown to be susceptible to penicillin, amoxicillin 500 mg (25 to 30 mg/kg for children) tid is an option when ciprofloxacin and doxycycline are contraindicated.

The Centers for Disease Control and Prevention (CDC) recommends that the anthrax vaccine be administered with antibiotic prophylaxis to patients exposed to anthrax spores. Postexposure antibiotic treatment is extended to 100 days in patients who are vaccinated.

Diphtheria

Diphtheria is an acute pharyngeal or cutaneous infection by *Corynebacterium diphtheriae*; some strains produce an exotoxin. Symptoms are either nonspecific skin infections or pseudomembranous pharyngitis followed by myocardial and neural tissue damage secondary to the exotoxin. Diagnosis is clinical and confirmed by culture. Treatment is with antitoxin and penicillin or erythromycin. Childhood vaccination should be routine.

Corynebacterium diphtheriae usually infect the nasopharynx (respiratory diphtheria) or skin.

Diphtheria toxin: Diphtheria strains infected by a β-phage, which carries a toxin-encoding gene, produce a potent toxin. This toxin first causes inflammation and necrosis of local tissues and then can damage the heart, nerves, and sometimes the kidneys. Nontoxigenic strains of *C. diphtheriae* can also cause nasopharyngeal infection and sometimes systemic disease (eg, endocarditis, septic arthritis).

Epidemiology and transmission: Humans are the only known reservoir for *C. diphtheriae*. The organism is spread by

• Respiratory droplets

• Contact with nasopharyngeal secretions

• Contact with infected skin lesions

• Fomites (rare)

A carrier state is common in endemic regions but not in developed countries; most patients who are adequately treated do not become carriers. Patients with clinical illness or asymptomatic carriers may transmit the infection.

Poor personal and community hygiene contributes to the spread of cutaneous diphtheria. In the US, indigent adults living in endemic areas are particularly at risk.

Diphtheria is endemic in many counties in Africa, South America, South and Southeast Asia, the Middle East, Haiti, and the Dominican Republic (travel information about diphtheria is available at the Centers for Disease Control and Prevention [CDC] web site). Diphtheria is now rare in developed countries because childhood immunization is widespread. However, after the breakup of the former Soviet Union, vaccination rates in its constituent countries fell, followed by a marked rise in diphtheria cases.

Symptoms and Signs

Symptoms vary depending on where the infection is and on whether the strain produces toxin. Most respiratory infections are caused by toxigenic strains. Cutaneous infections are caused by toxigenic and nontoxigenic strains. Toxin is poorly absorbed from the skin; thus, toxin complications are rare in cutaneous diphtheria.

Pharyngeal infection: After an incubation period, which averages 5 days, and a prodromal period of between 12 and 24 h, patients develop mild sore throat, dysphagia, low-grade fever, and tachycardia.

Nausea, emesis, chills, headache, and fever are more common among children.

If a toxigenic strain is involved, the characteristic membrane appears in the tonsillar area. It may initially appear as a white, glossy exudate but typically becomes dirty gray, tough, fibrinous, and adherent so that removal causes bleeding. Local edema may cause a visibly swollen neck (bull neck), hoarseness, stridor, and dyspnea. The membrane may extend to the larynx, trachea, and bronchi and may partially obstruct the airway or suddenly detach, causing complete obstruction.

Mild disease with a serosanguineous or purulent discharge and irritation of the external nares and upper lip occurs in patients who have only nasal diphtheria.

Skin infection: Skin lesions usually occur on the extremities and are varied in appearance, often indistinguishable from chronic skin conditions (eg, eczema, psoriasis, impetigo). A few patients have nonhealing, punched-out ulcers, occasionally with a grayish membrane. Pain, tenderness, erythema, and exudate are typical. If exotoxin is produced, lesions may be numb. Concomitant nasopharyngeal infection occurs in 20 to 40% by direct or indirect inoculation with the organism, often from preexisting chronic skin lesions.

Complications: The main complications are cardiac and neurologic.

Myocarditis is usually evident by the 10th to 14th day but can appear any time during the 1st to 6th wk, even while local respiratory symptoms are subsiding; risk of cardiac toxicity is related to degree of local infection. Insignificant ECG changes occur in 20 to 30% of patients, but atrioventricular dissociation, complete heart block, and ventricular arrhythmias may occur and are associated with a high mortality rate. Heart failure may develop.

Nervous system toxicity is uncommon (about 5%) and limited to patients with severe respiratory diphtheria. The toxin causes a demyelinating polyneuropathy that affects cranial and peripheral nerves. The toxic effects usually begin during the 1st wk of illness with loss of ocular accommodation and bulbar palsy, causing dysphagia and nasal regurgitation. Peripheral neuropathy appears during the 3rd to 6th wk. It is both motor and sensory, although motor symptoms predominate. Resolution occurs over many weeks.

Diagnosis

• Gram stain and culture

Diphtheria needs to be considered in patients with nonspecific findings of pharyngitis, cervical adenopathy, and low-grade fever if they also have systemic toxicity plus hoarseness, palatal paralysis, or stridor. The appearance of the characteristic membrane suggests the diagnosis.

Gram stain of the membrane may reveal gram-positive bacilli with metachromatic (beaded) staining in typical Chinese-character configuration. Material for culture should be obtained from below the membrane, or a portion of membrane itself should be submitted. The laboratory should be notified that *C. diphtheriae* is suspected, so that special culture media (Loeffler's or Tindale's) can be used. In vitro testing for toxin production (modified Elek test) is done to differentiate toxigenic from nontoxigenic strains.

Cutaneous diphtheria should be considered when a patient develops skin lesions during an outbreak of respiratory diphtheria. Swab or biopsy specimens should be cultured. Patients with cutaneous diphtheria may be co-infected with group A streptococci or *Staphylococcus aureus*.

Treatment

• Diphtheria antitoxin

• Penicillin or erythromycin

Symptomatic patients with respiratory diphtheria should be hospitalized in an ICU to monitor for

respiratory and cardiac complications. Isolation with respiratory-droplet and contact precautions is required and must continue until 2 cultures, taken 24 and 48 h after antibiotics are stopped, are negative.

Diphtheria antitoxin must be given without waiting for culture confirmation because the antitoxin neutralizes only toxin not yet bound to cells. The use of antitoxin for cutaneous disease, without evidence of respiratory disease, is of questionable value because toxic sequelae have rarely been reported in cutaneous diphtheria; however, some experts recommend it. In the US, antitoxin must be obtained from the CDC at 770-488-7100 (see also the CDC's notice regarding availability of diphtheria antitoxin). CAUTION: Diphtheria antitoxin is derived from horses; therefore, a skin (or conjunctival) test to rule out sensitivity should always precede administration (see p. 1115). The dose, ranging from 20,000 to 100,000 units IM or IV, is determined by the site and severity of symptoms, duration of the disease, and complications. If an allergic reaction occurs, 0.3 to 1 mL epinephrine 1:1000 (0.01 mL/kg) should immediately be injected sc, IM, or slowly IV. In highly sensitive patients, IV administration of antitoxin is contraindicated.

Antibiotics are required to eradicate the organism and prevent spread; they are not substitutes for antitoxin. Adults may be given either procaine penicillin G 600,000 units IM q 12 h or erythromycin 250 to 500 mg IV or po q 6 h for 14 days. Children should be given procaine penicillin G 12,500 to 25,000 units/kg IM q 12 h or erythromycin 10 to 15 mg/kg (maximum, 2 g/day) po or IV q 6 h. Organism elimination should be documented by 2 consecutive negative throat and/or nasopharyngeal cultures after completion of antibiotics.

Vaccination is required after recovery for patients who had diphtheria because infection does not guarantee immunity.

Recovery from severe diphtheria is slow, and patients must be advised against resuming activities too soon. Even normal physical exertion may harm patients recovering from myocarditis. Overall mortality is 3%; it is higher in those with delayed presentation or myocarditis and in children < 15 yr.

For cutaneous diphtheria, thorough cleansing of the lesion with soap and water and administration of systemic antibiotics for 10 days are recommended.

Prevention

Prevention consists of infection control measures plus

• Vaccination (primary and postexposure)

• Antibiotics

Vaccination: The vaccine for diphtheria contains diphtheria toxoid; it is available only in combination with other vaccines.

Everyone should be vaccinated at prescribed intervals using diphtheria-tetanus-acellular pertussis (DTaP) vaccine for children and tetanus-diphtheria (Td) or tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) for adolescents and adults (see p. 1173). (See also the CDC's National Immunization Program 2009 Childhood and Adolescent Immunization Schedule and their Adult Immunization Recommendations.)

After exposure, diphtheria immunization should be updated in all contacts (including hospital personnel) who have not completed a primary series or who have gone > 5 yr since their last booster dose. The vaccine should also be given if immunization status is unknown. An age-appropriate diphtheria toxoid-containing vaccine is used.

Postexposure antibiotics: All close contacts should be examined; surveillance for evidence of disease is maintained for 7 days. Nasopharyngeal and throat cultures for *C. diphtheriae* should be done regardless of immunization status.

Asymptomatic contacts should be treated with erythromycin 250 to 500 mg (10 to 15 mg/kg for children) po q 6 h for 7 days or, if adherence is uncertain, a single dose of penicillin G benzathine (600,000 units IM for patients < 30 kg and 1.2 million units IM for those > 30 kg).

If cultures are positive, an additional 10-day course of erythromycin should be given; carriers should not be given antitoxin. After 3 days of treatment, carriers can safely resume work while continuing to take antibiotics. Cultures should be repeated; 24 h after the completion of antimicrobial therapy, 2 consecutive culture sets of the nose and throat should be collected 24 h apart. If results are positive, another course of antibiotics is given and cultures are done again.

Erysipelothricosis

Erysipelothricosis is infection caused by *Erysipelothrix rhusiopathiae*. The most common symptom is erysipeloid, an acute but slowly evolving localized cellulitis. Diagnosis is by culture of a biopsy specimen or occasionally PCR testing. Treatment is with antibiotics.

Erysipelothrix rhusiopathiae (formerly *E. insidiosa*) are capsulated, nonsporulating, nonmotile, microaerophilic bacilli with worldwide distribution; they are primarily saprophytes. They may infect a variety of animals, including insects, shellfish, fish, birds, and mammals (especially swine). In humans, infection is chiefly occupational and typically follows a penetrating wound in people who handle edible or nonedible animal matter (eg, infected carcasses, rendered products [grease, fertilizer], bones, shells). Most commonly, patients handle fish or work in slaughterhouses. Infection can also result from cat or dog bites. Nondermal infection is rare, usually occurring as arthritis or endocarditis.

Symptoms and Signs

Within 1 wk of injury, a characteristic raised, purplish red, nonvesiculated, indurated, maculopapular rash appears, accompanied by itching and burning. Local swelling, although sharply demarcated, may inhibit use of the hand, the usual site of infection. The lesion's border may slowly extend outward, causing discomfort and disability that may persist for 3 wk. The disease is usually self-limited. Regional lymphadenopathy occurs in about one third of cases. It rarely becomes generalized cutaneous disease, which is characterized by purple skin lesions that expand as the lesion's center clears, plus bullous lesions at the primary or distant sites.

Bacteremia is rare and is more often a primary infection than dissemination from cutaneous lesions. It may result in septic arthritis or infective endocarditis, even in people without known valvular heart disease. Endocarditis tends to involve the aortic valve, and the mortality rate and percentage of patients needing cardiac valve replacement are unusually high.

Diagnosis

• Culture

Culture of a full-thickness biopsy specimen is superior to needle aspiration of the advancing edge of a lesion because organisms are located only in deeper parts of the skin. Culture of exudate obtained by abrading a florid papule may be diagnostic. Isolation from synovial fluid or blood is necessary for diagnosis of erysipelothrical arthritis or endocarditis. *E. rhusiopathiae* may be misidentified as lactobacilli or enterococci. PCR amplification may aid rapid diagnosis.

Treatment

• Penicillin, ciprofloxacin, or erythromycin

For **localized cutaneous disease**, usual treatment is penicillin V, ampicillin, ciprofloxacin, or erythromycin (macrolides may not be consistently active) 500 mg po qid for 7 days. Tetracyclines and cephalosporins are also effective. *E. rhusiopathiae* are resistant to sulfonamides and vancomycin.

Severe diffuse cutaneous or systemic infection is best treated with IV penicillin G (12 to 20 million

units/day), ceftriaxone (2 g IV once/day), or a fluoroquinolone (eg, ciprofloxacin 400 mg IV q 12 h).

Endocarditis is treated with penicillin G 25,000 to 30,000 units/kg IV q 4 h for 4 wk. Cephalosporins and fluoroquinolones are alternatives.

The same drugs and doses are appropriate for arthritis (given for at least 1 wk after defervescence or cessation of effusion), but repeated needle aspiration drainage of the infected joint is also necessary.

Listeriosis

(See also Neonatal Listeriosis on p. .)

Listeriosis is bacteremia, meningitis, cerebritis, dermatitis, an oculoglandular syndrome, intrauterine and neonatal infections, or rarely endocarditis caused by *Listeria* sp. Symptoms vary with the organ system affected and include intrauterine death in perinatal infection. Diagnosis is by laboratory isolation. Treatment includes penicillin, ampicillin (often with aminoglycosides), and trimethoprim/sulfamethoxazole.

Listeria are small, non-acid-fast, noncapsulated, nonsporulating, β-hemolytic, aerobic, and facultative anaerobic gram-positive bacilli that have characteristic tumbling motility. They are present worldwide in the environment and in the gut of humans, nonhuman mammals, birds, arachnids, and crustaceans. There are several species of *Listeria*, but *L. monocytogenes* is the only pathogen in humans. Incidence in the US is ≥ 7 cases/1,000,000 people/yr, peaking in the summer; attack rates are highest in neonates and in adults ≥ 60 yr.

Because *L. monocytogenes* is ubiquitous in the environment, opportunities for contamination are numerous during the food production process. Infection usually occurs via ingestion of contaminated dairy products, raw vegetables, or meats and is favored by the ability of *L. monocytogenes* to survive and grow at refrigerator temperatures. Infection may also occur by direct contact and during slaughter of infected animals.

Risk factors: Glucocorticoid therapy is the most important predisposing factor in nonpregnant adults. Because *L. monocytogenes* multiplies intracellularly, control of listeriosis requires cell-mediated immunity; thus, immunocompromised patients are at high risk. Pregnant women are also at increased risk of developing listerial infection, which can spread antepartum and intrapartum from mother to child and can cause abortion or early infant death.

Symptoms and Signs

Primary listerial bacteremia is rare and causes high fever without localizing symptoms and signs. Endocarditis, peritonitis, osteomyelitis, cholecystitis, and pleuropneumonia may occur. Listerial bacteremia during pregnancy can cause intrauterine infection, chorioamnionitis, premature labor, fetal death, or neonatal infections.

Meningitis is due to *Listeria* in about 20% of cases in neonates and in patients > 60 yr. Twenty percent of cases progress to cerebritis, either diffuse encephalitis or, rarely, rhombencephalitis and abscesses; rhombencephalitis manifests as altered consciousness, cranial nerve palsies, cerebellar signs, and motor or sensory loss.

Oculoglandular listeriosis can cause ophthalmitis and regional lymph node enlargement. It may follow conjunctival inoculation and, if untreated, may progress to bacteremia and meningitis.

Diagnosis

• Culture

Listerial infections are diagnosed by culture of blood or CSF. The laboratory must be informed when *L. monocytogenes* is suspected because the organism is easily confused with diphtheroids. In all listerial

infections, IgG agglutinin titers peak 2 to 4 wk after onset.

Treatment

• Ampicillin, usually with an aminoglycoside

Listerial meningitis is best treated with ampicillin 2 g IV q 4 h. Most authorities recommend adding an aminoglycoside based on synergy in vitro. Children receive ampicillin 50 to 100 mg/kg IV q 6 h. Cephalosporins are not effective.

Endocarditis and primary listerial bacteremia are treated with ampicillin 2 g IV q 4 h plus gentamicin (for synergy) given for 6 wk (for endocarditis) or 2 wk (for bacteremia) beyond defervescence. Oculoglandular listeriosis and listerial dermatitis should respond to erythromycin 10 mg/kg po q 6 h, continued until 1 wk after defervescence. Cephalosporins have no in vitro activity and should not be used. Trimethoprim/sulfamethoxazole 5/25 mg/kg IV q 8 h is an alternative.

Nocardiosis

Nocardiosis is an acute or chronic, often disseminated, suppurative or granulomatous infection caused by various aerobic soil saprophytes of the genus *Nocardia*. Pneumonia is typical, but skin and CNS infections are common. Diagnosis is by culture and special stains. Treatment is usually with sulfonamides.

Nocardia are obligate aerobic, partially acidfast, beaded, branching, gram-positive bacilli. Several *Nocardia* sp, in the family Actinomycetaceae, cause human disease.

N. asteroides is the most common human pathogen; it usually causes pulmonary and disseminated infection.

N. brasiliensis most commonly causes skin infection, particularly in tropical climates. Infection is via inhalation or by direct inoculation of the skin.

Other *Nocardia* sp sometimes cause localized or, occasionally, systemic infections.

Nocardiosis occurs worldwide in all age groups, but incidence is higher in older adults, especially men. Person-to-person spread is rare.

Risk factors: Lymphoreticular cancers, organ transplantation, high-dose corticosteroid or other immunosuppressive therapy, and underlying pulmonary disease are predisposing factors, but about one half of patients have no preexisting disease. Nocardiosis is also an opportunistic infection in patients with advanced HIV infection.

Symptoms and Signs

Nocardiosis usually begins as a subacute pulmonary infection that resembles actinomycosis, but *Nocardia* are more likely to disseminate locally or hematogenously. Dissemination with abscess formation may involve any organ but most commonly affects the brain, skin, kidneys, bone, or muscle.

The most common symptoms of pulmonary involvement—cough, fever, chills, chest pain, weakness, anorexia, and weight loss—are nonspecific and may resemble those of TB or suppurative pneumonia. Pleural effusion may also occur. Metastatic brain abscesses, occurring in 30 to 50% of cases, usually cause severe headaches and focal neurologic abnormalities. Infection may be acute, subacute, or chronic.

Skin or subcutaneous abscesses occur frequently, sometimes as a primary local inoculation. They may appear as firm cellulitis, a lymphocutaneous syndrome, or an actinomycetoma. The lymphocutaneous syndrome consists of a primary pyoderma lesion and lymphatic nodules resembling sporotrichosis. An actinomycetoma begins as a nodule, suppurates, spreads along fascial planes, and drains through

chronic fistulas.

Diagnosis

• Microscopic examination or culture

Diagnosis is by identification of *Nocardia* sp in tissue or in culture of samples from localized lesions identified by physical examination, x-ray, or other imaging studies. Clumps of beaded, branching filaments of gram-positive bacteria (which may be weakly acid-fast) are often seen. *Nocardia* do not have a clubbed appearance, as do *Actinomyces israelii*.

Prognosis

Without treatment, pulmonary and disseminated nocardiosis are usually fatal. Among patients who are treated with appropriate antibiotics, the mortality rate is highest (> 50%) in immunocompromised patients with disseminated infections and lowest (about 10%) in immunocompetent patients with lesions restricted to the lungs. Cure rates for patients with skin infection are usually > 95%.

Treatment

• Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole or high doses of a sulfonamide alone (sulfamethoxazole or sulfisoxazole) are used. Because most cases respond slowly, a dose that maintains a sulfonamide blood concentration of 12 to 15 mg/dL (eg, with sulfadiazine 4 to 6 g/day po) must be continued for several months.

When sulfonamide hypersensitivity or refractory infection is present, amikacin, a tetracycline (particularly minocycline), imipenem/cilastatin, ceftriaxone, cefotaxime, extended-spectrum fluoroquinolones (eg, moxifloxacin), or cycloserine can be used. In vitro susceptibility data should guide the choice of alternative drugs.

Chapter 135. Gram-Negative Bacilli

Introduction

Gram-negative bacilli are responsible for numerous diseases. Some are commensal organisms present among normal intestinal flora. These commensal organisms plus others from animal or environmental reservoirs may cause disease. UTIs, diarrhea, peritonitis, and bloodstream infections are commonly caused by gram-negative bacilli. Plague, cholera, and typhoid fever are rare but serious gram-negative infections.

Bartonella Infections

Bartonella sp are gram-negative bacteria previously classified as Rickettsiae. They cause several uncommon diseases: cat-scratch disease, an acute febrile anemia, a chronic cutaneous eruption, and disseminated disease in immunocompromised hosts (see Table 135-1).

Cat-Scratch Disease

(Cat-Scratch Fever)

Cat-scratch disease is infection caused by *Bartonella henselae*. Symptoms are a local papule and regional lymphadenitis. Diagnosis is clinical and confirmed by biopsy. Treatment is with local heat application and analgesics.

The domestic cat is a major reservoir for *B. henselae*. The prevalence of *B. henselae* antibodies in US cats is 14 to 50%. About 99% of patients report contact with cats, most of which are healthy. The cat flea may be an additional vector. Children are most often affected.

Symptoms and Signs

Within 3 to 10 days after a scratch, most patients develop an erythematous, crusted papule (rarely, a pustule) at the scratch site. Regional lymphadenopathy develops within 2 wk. The nodes are initially firm and tender, later becoming fluctuant, and may drain with fistula formation. Fever, malaise, headache, and anorexia may accompany lymphadenopathy.

Unusual manifestations occur in 5 to 14% of patients: Parinaud's oculoglandular syndrome (conjunctivitis associated with palpable preauricular nodes) in 6%, neurologic manifestations (encephalopathy, seizures, neuroretinitis, myelitis, paraplegia, cerebral arteritis) in 2%, and hepatosplenic granulomatous disease in

[**Table 135-1.** Some *Bartonella* Infections]

< 1%. Severe disseminated illness may occur in patients with AIDS.

Lymphadenopathy subsides spontaneously within 2 to 5 mo. Complete recovery is usual, except in severe neurologic or hepatosplenic disease, which may be fatal or have residual effects.

Diagnosis

Diagnosis is confirmed by positive serum Ab titers or PCR testing of samples from lymph node aspirates. Immunocompromised patients and patients with systemic symptoms should also have blood cultures. Lymph node aspirates are rarely culture-positive.

Treatment

• Local heat and analgesics

• Sometimes antibiotics for immunocompromised patients

Treatment in immunocompetent patients is local heat application and analgesics. If a lymph node is fluctuant, needle aspiration usually relieves the pain.

Antibiotic treatment is not clearly beneficial and generally should not be given for localized infection. Ciprofloxacin, gentamicin, or doxycycline may be used for bacteremia in AIDS patients. Prolonged therapy is usually necessary (eg, weeks to months) for bacteremia to clear. In vitro antibiotic susceptibilities often do not correlate with clinical results; testing often shows sensitivity to trimethoprim/sulfamethoxazole (TMP/SMX) and cephalosporins, but these drugs are clinically ineffective.

Oroya Fever and Verruga Peruana

Oroya fever and verruga peruana are infections caused by *Bartonella bacilliformis*. Oroya fever occurs after initial exposure; verruga peruana occurs after recovery from the primary infection.

Endemic only to the Andes Mountains in Colombia, Ecuador, and Peru, both diseases are passed from human to human by the *Phlebotomus* sandfly.

Oroya fever: Symptoms include fever and profound anemia, which may be sudden or indolent in onset. The anemia is primarily hemolytic, but myelosuppression also occurs. Muscle and joint pain, severe headache, and often delirium and coma may occur. Superimposed bacteremia caused by *Salmonella* or other coliform organisms may occur. Mortality rates may exceed 50% in untreated patients.

Diagnosis is confirmed by blood cultures. Because Oroya fever is often complicated by *Salmonella* bacteremia, chloramphenicol 500 to 1000 mg po q 6 h for 7 days is the treatment of choice; some clinicians add another antibiotic, typically a β-lactam, but TMP/SMX, macrolides, and fluoroquinolones have also been used successfully.

Verruga peruana: This disorder manifests as multiple skin lesions that strongly resemble bacillary angiomatosis, usually occurring on the limbs and face. The lesions may persist for months to years and may be accompanied by pain and fever.

Verruga peruana is diagnosed by its appearance and sometimes by biopsy showing dermal angiogenesis. Treatment with most antibiotics produces remission, but relapse is common and requires prolonged therapy. Typical treatment is streptomycin 15 to 20 mg/kg IM once/day for 10 days or rifampin 10 mg/kg po once/day for 10 to 14 days. Ciprofloxacin 500 mg po bid for 7 to 10 days has been used successfully, as has azithromycin.

Bacillary Angiomatosis

(Epithelioid Angiomatosis)

Bacillary angiomatosis is skin infection caused by *Bartonella henselae* or *B. quintana*.

Bacillary angiomatosis almost always occurs in immunocompromised people and is characterized by protuberant, reddish, berry-like lesions on the skin, often surrounded by a collar of scale. Lesions bleed profusely if traumatized. They may resemble Kaposi's sarcoma or pyogenic granulomas. Infection is spread by lice and ticks and probably by fleas from household cats. Disease may spread throughout the reticuloendothelial system, particularly in AIDS patients.

Diagnosis relies on histopathology of the skin lesions, cultures, and PCR analysis. The laboratory should be notified that *Bartonella* is suspected because special stains and prolonged culture growth are necessary.

Treatment is with erythromycin 500 mg po q 6 h or doxycycline 100 mg po q 12 h, continued for at least 3 mo.

Trench Fever

(Wolhynia, Shin Bone, or Quintan Fever)

Trench fever is a louse- or tick-borne disease caused by *Bartonella quintana* or *B. henselae* and observed originally in military populations during World Wars I and II. Symptoms are an acute, recurring febrile illness, occasionally with a rash. Diagnosis is by blood culture. Treatment is with a macrolide or doxycycline.

Humans are the only reservoir. *B. quintana* is transmitted to humans when feces from infected lice are rubbed into abraded skin or the conjunctiva. *B. henselae* is transmitted by tick bites. Trench fever is endemic in Mexico, Tunisia, Eritrea, Poland, and the former Soviet Union and is reappearing in the homeless population in the US.

After a 14- to 30-day incubation period, onset is sudden, with fever, weakness, dizziness, headache, and severe back and leg pains. Fever may reach 40.5° C and persist for 5 to 6 days. In about half the cases, fever recurs 1 to 8 times at 5- to 6-day intervals. A transient macular or papular rash and, occasionally, hepatomegaly and splenomegaly occur. Relapses are common and have occurred up to 10 yr after the initial attack.

Diagnosis

Trench fever should be suspected in people living where louse infestation is heavy. Leptospirosis, typhus, relapsing fever, and malaria must be considered.

The organism is identified by blood culture, although growth may take 1 to 4 wk. The disease is marked by persistent bacteremia during the initial attack, during relapses, and throughout the asymptomatic periods between relapses.

Treatment

Although recovery is usually complete in 1 to 2 mo and mortality is negligible, bacteremia may persist for months after clinical recovery, and prolonged (> 1 mo) macrolide or doxycycline treatment may be needed. Body lice must be controlled (see p.). Patients with chronic bacteremia should be monitored for signs of endocarditis.

Brucellosis

(Undulant, Malta, Mediterranean, or Gibraltar Fever)

Brucellosis is caused by *Brucella* sp. Symptoms begin as an acute febrile illness with few or no localized signs and progress to a chronic stage with relapses of fever, weakness, sweats, and vague aches and pains. Diagnosis is by culture, usually from the blood. Optimal treatment usually requires 2 antibiotics—doxycycline or trimethoprim/sulfamethoxazole plus streptomycin or rifampin.

The causative organisms of human brucellosis are *B. abortus* (from cattle), *B. melitensis* (from sheep and goats), and *B. suis* (from hogs). *B. canis* (from dogs) has caused sporadic infections. The most common sources of infection are farm animals and raw dairy products. Deer, bison, horses, moose, caribou, hares, chickens, and desert rats may also be infected; humans can acquire the infection from these animals as well.

Brucellosis is acquired by direct contact with secretions and excretions of infected animals and by ingesting undercooked meat, raw milk, or milk products containing viable organisms. Brucellosis is rarely transmitted from person to person. Most prevalent in rural areas, brucellosis is an occupational disease of meatpackers, veterinarians, hunters, farmers, and livestock producers. Brucellosis is rare in the US, Europe, and Canada, but cases occur in the Middle East, Mediterranean regions, Mexico, and Central America.

Patients with acute, uncomplicated brucellosis usually recover in 2 to 3 wk, even without treatment. Some go on to subacute, intermittent, or chronic disease.

Complications: Complications are rare but include subacute bacterial endocarditis, meningitis, encephalitis, neuritis, orchitis, cholecystitis, hepatic suppuration, and osteomyelitis (particularly sacroiliac or vertebral).

Symptoms and Signs

The incubation period varies from 5 days to several months and averages 2 wk. Onset may be sudden, with chills and fever, severe headache, joint and low back pain, malaise, and occasionally diarrhea. Or onset may be insidious, with mild prodromal malaise, muscular pain, headache, and pain in the back of the neck, followed by a rise in evening temperature. As the disease progresses, temperature increases to 40 to 41° C, then subsides gradually to normal or near-normal with profuse sweating in the morning.

Typically, intermittent fever persists for 1 to 5 wk, followed by a 2- to 14-day remission when symptoms are greatly diminished or absent. In some patients, fever may be transient. In others, the febrile phase recurs once or repeatedly in waves (undulations) and remissions over months or years and may manifest as FUO.

After the initial febrile phase, anorexia, weight loss, abdominal and joint pain, headache, backache, weakness, irritability, insomnia, depression, and emotional instability may occur. Constipation is usually pronounced. Splenomegaly appears, and lymph nodes may be slightly or moderately enlarged. Up to 50% of patients have hepatomegaly.

Diagnosis

• Blood cultures

• Acute and convalescent serologic testing

Blood cultures should be obtained; growth may take > 7 days, so the laboratory should be notified of the suspicion of brucellosis.

Acute and convalescent sera should be obtained 3 wk apart. A 4-fold increase or an acute titer of 1:160 or higher is considered diagnostic, particularly if a history of exposure and characteristic clinical findings are present. The WBC count is normal or reduced with relative or absolute lymphocytosis during the acute phase.

Treatment

• Doxycycline plus streptomycin

Activity should be restricted in acute cases, with bed rest recommended during febrile episodes.

If antibiotics are given, combination therapy is preferred. Doxycycline 100 mg po bid for 3 to 6 wk plus streptomycin 1 g IM q 12 to 24 h for 14 days lowers the rate of relapses. In children < 8 yr, trimethoprim/sulfamethoxazole (TMP/SMX) and either IM streptomycin or oral rifampin for 4 to 6 wk have been used. Severe musculoskeletal pains, especially over the spine, may require analgesia.

Pasteurization of milk helps prevent brucellosis. Cheese that is made from unpasteurized milk and is aged < 3 mo may be contaminated. People handling animals or carcasses likely to be infected should wear goggles and rubber gloves and protect skin breaks from exposure. Programs to detect infection in animals, eliminate infected animals, and vaccinate young seronegative cattle and swine are required in the US and in several other countries. Immunity after human infection is short-lived, lasting about 2 yr.

Campylobacter and Related Infections

***Campylobacter* infections commonly cause diarrhea and occasionally bacteremia, with consequent endocarditis, osteomyelitis, or septic arthritis.**

Campylobacter sp are motile, curved, microaerophilic, gram-negative bacilli that normally inhabit the GI tract of many domestic animals and fowl. Several species are human pathogens. The major pathogens are *C. jejuni* and *C. fetus. C. jejuni* causes diarrhea in all age groups, although peak incidence appears to be from age 1 to 5 yr. *C. jejuni* accounts for more cases of diarrhea in the US than *Salmonella* and *Shigella* combined. *C. fetus* and several others typically cause bacteremia in adults, more often when underlying predisposing diseases, such as diabetes, cirrhosis, or cancer, are present. In patients with immunoglobulin deficiencies, these organisms may cause difficult-to-treat, relapsing infections. *C. jejuni* can cause meningitis in infants.

Contact with infected animals and ingestion of contaminated food (especially under-cooked poultry) or water have been implicated in outbreaks. However, in sporadic cases, the source of the infecting organism is frequently obscure.

Complications: *C. jejuni* diarrheal illness is associated with subsequent development (up to 30% of cases) of Guillain-Barre syndrome because of cross-reaction between *C. jejuni* antibodies and surface components of peripheral nerves.

Postinfectious (reactive) arthritis may occur in HLA-B27-positive patients a few days to several weeks after an episode of *C. jejuni* diarrhea.

Focal extraintestinal infections (eg, endocarditis, meningitis, septic arthritis) occur rarely.

Symptoms and Signs

The most common manifestation is watery and sometimes bloody diarrhea. Fever (38 to 40° C), which follows a relapsing or intermittent course, is the only constant feature of systemic *Campylobacter* infection, although abdominal pain and hepatosplenomegaly are frequent.

Patients can also present with subacute bacterial endocarditis, reactive arthritis, meningitis, or an indolent FUO rather than with diarrheal illness. Joint involvement with reactive arthritis is usually monoarticular, affecting the knees; symptoms resolve spontaneously over 1 wk to several months.

Diagnosis

• Stool culture

• Sometimes blood cultures

Diagnosis, particularly to differentiate *Campylobacter* infection from ulcerative colitis (see p.), requires microbiologic evaluation. Stool culture should be obtained plus blood cultures for patients with signs of focal infection or serious systemic illness. WBCs are present in stained smears of stool.

Treatment

• Sometimes erythromycin

Most enteric infections resolve spontaneously; if they do not, erythromycin 500 mg po q 6 h for 5 days may be helpful. For patients with extraintestinal infections, antibiotics (eg, imipenem, gentamicin, ampicillin, erythromycin) should be given for 2 to 4 wk to prevent relapses.

Cholera

Cholera is an acute infection of the small bowel by *Vibrio cholerae*, which secretes a toxin that causes copious watery diarrhea, leading to dehydration, oliguria, and circulatory collapse.

Infection is typically through contaminated water or seafood. Diagnosis is by culture or serology. Treatment is vigorous rehydration and electrolyte replacement plus doxycycline.

The causative organism, *V. cholerae*, serogroups 01 and 0139, is a short, curved, motile, aerobic bacillus that produces enterotoxin, a protein that induces hypersecretion of an isotonic electrolyte solution by the small-bowel mucosa. Both the El Tor and classic biotypes of *V. cholerae* can cause severe disease. However, mild or asymptomatic infection is much more common with the El Tor biotype.

Cholera is spread by ingestion of water, seafood, or other foods contaminated by the excrement of people with symptomatic or asymptomatic infection. Cholera is endemic in portions of Asia, the Middle East, Africa, South and Central America, and the Gulf Coast of the US. Cases transported into Europe, Japan, and Australia have caused localized outbreaks. In endemic areas, outbreaks usually occur during warm months. The incidence is highest in children. In newly affected areas, epidemics may occur during any season, and all ages are equally susceptible. A milder form of gastroenteritis is caused by noncholera vibrios (see p.).

Susceptibility to infection varies and is greater for people with blood type O. Because vibrios are sensitive to gastric acid, hypochlorhydria and achlorhydria are predisposing factors. People living in endemic areas gradually acquire a natural immunity.

Symptoms and Signs

The incubation period is 1 to 3 days. Cholera can be subclinical, a mild and uncomplicated episode of diarrhea, or a fulminant, potentially lethal disease. Abrupt, painless, watery diarrhea and vomiting are usually the initial symptoms. Significant nausea is typically absent. Stool loss in adults may exceed 1 L/h but is usually much less. The resultant severe water and electrolyte depletion leads to intense thirst, oliguria, muscle cramps, weakness, and marked loss of tissue turgor, with sunken eyes and wrinkling of skin on the fingers. Hypovolemia, hemoconcentration, oliguria and anuria, and severe metabolic acidosis with K+ depletion (but normal serum Na+ concentration) occur. If cholera is untreated, circulatory collapse with cyanosis and stupor may follow. Prolonged hypovolemia can cause renal tubular necrosis.

Most patients are free of *V. cholerae* within 2 wk after cessation of diarrhea; chronic biliary tract carriers are rare.

Diagnosis

• Stool culture and serotyping

Diagnosis is confirmed by stool culture and subsequent serotyping. Cholera can be distinguished from clinically similar disease caused by enterotoxin-producing strains of *Escherichia coli* and occasionally by *Salmonella* and *Shigella*. Serum electrolytes, BUN, and creatinine should be measured.

Treatment

• Fluid replacement

• Doxycycline, furazolidone, or trimethoprim/sulfamethoxazole (TMP/SMX), depending on results of susceptibility testing

Replacement of fluid loss is essential. Mild cases can be treated with standard oral replacement formulas (see p.). Rapid correction of severe hypovolemia is lifesaving. Prevention or correction of metabolic acidosis and hypokalemia is important. For hypovolemic and severely dehydrated patients, IV replacement with isotonic fluids should be used (for details on fluid resuscitation, see pp. and). Water should also be given freely by mouth. To replace K+ losses, KCl 10 to 15 mEq/L can be added to the IV solution, or $KHCO_3$ 1 mL/kg po of a 100-g/L solution can be given qid. K+ replacement is especially important for children, who tolerate hypokalemia poorly.

Once intravascular volume is restored, amounts for replacement of continuing losses should equal measured stool volume. Adequacy of hydration is confirmed by frequent clinical evaluation (pulse rate and strength, skin turgor, urine output). Plasma, plasma volume expanders, and vasopressors should *not* be used in place of water and electrolytes.

Oral glucose-electrolyte solution is effective in replacing stool losses and may be used after initial IV rehydration, and it may be the only means of rehydration in epidemic areas where supplies of parenteral fluids are limited. Patients who have mild or moderate dehydration and who can drink may be rehydrated exclusively with the oral solution (about 75 mL/kg in 4 h). Those with more severe dehydration need more and may need to receive the fluid by nasogastric tube. The oral solution recommended by the WHO contains 20 g glucose, 3.5 g NaCl, 2.9 g trisodium citrate and dihydrate (or 2.5 g NaHCO$_3$), and 1.5 g KCl per liter of drinking water. This solution should be continued ad libitum after rehydration in amounts at least equal to continuing stool and vomitus losses. Solid food should be given only after vomiting stops and appetite returns.

Early treatment with an effective oral antimicrobial eradicates vibrios, reduces stool volume by 50%, and stops diarrhea within 48 h. The choice of antimicrobial should be based on the susceptibility of *V. cholerae* isolated from the community.

Drugs effective for susceptible strains include

• Doxycycline: For adults, a single dose of 300 mg po

• Furazolidone: For adults, 100 mg po qid for 72 h; for children, 1.5 mg/kg qid for 72 h

• TMP/SMX: For adults, one double-strength tablet bid; for children, 5 mg/kg (of the TMP component) bid for 72 h

Prevention

For control of cholera, human excrement must be correctly disposed of, and water supplies purified. In endemic regions, drinking water should be boiled or chlorinated, and vegetables and fish cooked thoroughly.

A killed oral whole cell-B subunit vaccine (not available in the US) provides 85% protection against the 01 serogroup for 4 to 6 mo. Protection lasts up to 3 yr in adults but wanes rapidly in children and is greater for the classic than for the El Tor biotype. There is no cross-protection between 01 and 0139 serogroups. Vaccines proven effective against both sero-groups are a future goal. The parenteral cholera vaccine is not recommended because of its low efficacy, short duration (43% for 3 mo), and frequent severe adverse effects.

Prompt prophylaxis with doxycycline 100 mg po q 12 h in adults (TMP/SMX can be used for prophylaxis in children < 9 yr) can decrease secondary cases among household contacts of cholera patients, but mass prophylaxis is inappropriate and some strains are not sensitive.

Noncholera *Vibrio* Infections

Noncholera vibrios include *Vibrio parahaemolyticus, V. mimicus, V. alginolyticus, V. hollisae*, and *V. vulnificus*; these vibrios are sometimes called nonagglutinable vibrios (ie, they do not agglutinate with serum from cholera patients). They typically inhabit warm salt water or mixed salt and fresh water (eg, in estuaries).

V. parahaemolyticus, V. mimicus, and *V. hollisae* usually cause food-borne outbreaks of diarrhea, typically involving inadequately cooked seafood (usually shellfish). *V. parahaemolyticus* infections typically occur in Japan and in coastal areas of the US. The organisms damage intestinal mucosa but do not produce enterotoxin or invade the bloodstream. Also, wound infection may develop when

contaminated warm seawater enters a minor wound.

V. alginolyticus and *V. vulnificus* can cause serious wound infection; neither causes enteritis. *V. vulnificus*, when ingested by a compromised host (often someone with chronic liver disease or immunodeficiency), can cross the intestinal mucosa without causing enteritis and cause septicemia with a high mortality rate; occasionally, otherwise healthy people develop such infections.

Symptoms and Signs

After a 15- to 24-h incubation period, enteric illness begins suddenly with cramping abdominal pain, large amounts of watery diarrhea (stools may be bloody and contain PMNs), tenesmus, weakness, and sometimes nausea, vomiting, and low-grade fever. Symptoms subside spontaneously in 24 to 48 h.

Cellulitis can rapidly develop in contaminated wounds in some cases (typically those involving *V. vulnificus*) and progress to necrotizing fasciitis with typical hemorrhagic, bullous lesions.

V. vulnificus septicemia causes shock, bullous skin lesions, and often manifestations of disseminated intravascular coagulation (eg, thrombocytopenia, hemorrhage); mortality rate is high.

Diagnosis

• Cultures

Wound and bloodstream infections are readily diagnosed with routine cultures. When enteric infection is suspected, *Vibrio* organisms can be cultured from stool on thiosulfate citrate bile salts sucrose medium. Contaminated seafood also yields positive cultures.

Treatment

• Ciprofloxacin or doxycycline for enteric infection

• Antibiotics and often debridement for wound infection

Noncholera *Vibrio* enteric infections can be treated with a single dose of ciprofloxacin 1 g po or doxycycline 300 mg po. For diarrhea, close attention to volume repletion and replacement of lost electrolytes are needed.

For wound infections, antibiotics are used—typically, doxycycline 100 mg po q 12 h, with or without a 3rd-generation cephalosporin for severe wound infection or septicemia. Patients with necrotizing fasciitis require surgical debridement.

Escherichia Coli Infections

Escherichia coli are the most numerous aerobic commensal inhabitants of the large intestine. Certain strains cause diarrhea, and all can cause infection when they invade sterile sites (eg, the urinary tract). Diagnosis is by standard culture techniques. Toxin assays may help identify the cause of diarrhea. Treatment with antibiotics is guided by susceptibility testing.

Diseases caused by *E. coli*: Most commonly, *E. coli* cause UTIs, which usually represent ascending infection (ie, from the perineum via the urethra).

E. coli normally inhabit the GI tract; however, some strains have acquired genes that enable them to cause intestinal infection. When ingested, the following strains can cause diarrhea:

• Enterohemorrhagic: These strains (eg, type O157:H7—see below) produce several cytotoxins, neurotoxins, and enterotoxins, including Shiga toxin, and cause bloody diarrhea; hemolytic-uremic syndrome develops in 2 to 7% of cases (see p.). Such strains have most often been acquired from undercooked ground beef but may also be acquired from infected people by the fecaloral route when

hygiene is inadequate.

• Enterotoxigenic: These strains can cause watery diarrhea, particularly in infants and travelers (see p.).

• Enteroinvasive: These strains can cause inflammatory diarrhea.

• Enteropathogenic: These strains can cause watery diarrhea, particularly in infants.

• Enteroaggregative: Some strains are emerging as potentially important causes of persistent diarrhea in patients with AIDS and in children in tropical areas.

Other strains are capable of causing extra-intestinal infection if normal intestinal anatomic barriers are disrupted (eg, by ischemia, inflammatory bowel disease, or trauma), in which case the organism may spread to adjacent structures or invade the bloodstream. Hepatobiliary, peritoneal, cutaneous, and pulmonary infections also occur. *E. coli* bacteremia may also occur without an evident portal of entry.

In neonates, particularly preterm infants, *E. coli* bacteremia and meningitis (caused by strains with the K1 capsule, a marker for neuroinvasiveness) are common (see Neonatal Bacterial Meningitis on p. and Neonatal Sepsis on p.).

Diagnosis

• Culture

Samples of blood, stool, or other clinical material are sent for culture. If an enterohemorrhagic strain is suspected, the laboratory must be notified because special culture media are required.

Treatment

• Various antibiotics depending on site of infection and susceptibility testing

Treatment must be started empirically based on the site and severity of infection (eg, mild bladder infection, urosepsis) and then modified based on antibiotic susceptibility testing. Many strains are resistant to ampicillin and tetracyclines, so other drugs should be used; they include ticarcillin, piperacillin, cephalosporins, aminoglycosides, trimethoprim/sulfamethoxazole (TMP/SMX), and fluoroquinolones.

Surgery may be required to drain pus, debride necrotic lesions, or remove foreign bodies.

E. coli O157:H7 Infection

E. coli O157:H7 typically causes acute bloody diarrhea, which may lead to hemolytic-uremic syndrome. Symptoms are abdominal cramps and diarrhea that may be grossly bloody. Fever is not prominent. Diagnosis is by stool culture and toxin assay. Treatment is supportive; antibiotic use is controversial.

Epidemiology

Although > 100 serotypes of *E. coli* produce Shiga and Shiga-like toxins, *E. coli* O157:H7 is the most common in North America. In some parts of the US and Canada, *E. coli* O157:H7 infection may be a more common cause of bloody diarrhea than shigellosis or salmonellosis. *E. coli* O157:H7 infection can occur in people of all ages, although severe infection is most common among children and the elderly.

E. coli O157:H7 has a bovine reservoir, so outbreaks and sporadic cases occur after ingestion of undercooked beef (especially ground beef) or unpasteurized milk. Food or water contaminated with cow manure or raw ground beef can also transmit infection. The organism can also be transmitted by the fecal-oral route, especially among infants in diapers (eg, via inadequately chlorinated children's wading pools).

After ingestion, *E. coli* O157:H7 and similar strains of *E. coli* (termed enterohemorrhagic *E. coli*) produce high levels of various toxins in the large intestine; these toxins are closely related to the potent cytotoxins produced by *Shigella dysenteriae* type 1. These toxins appear to directly damage mucosal cells and vascular endothelial cells in the gut wall. If absorbed, they exert toxic effects on other vascular endothelia (eg, renal).

Symptoms and Signs

E. coli O157:H7 infection typically begins acutely with severe abdominal cramps and watery diarrhea that may become grossly bloody within 24 h. Some patients report diarrhea as being "all blood and no stool," which has given rise to the term hemorrhagic colitis. Fever, usually absent or low grade, occasionally reaches 39° C. Diarrhea may last 1 to 8 days in uncomplicated infections.

About 5% of cases (mostly children < 5 yr and adults > 60 yr) are complicated by hemolytic-uremic syndrome (see p.), which typically develops in the 2nd wk of illness. Death may occur, especially in the elderly, with or without this complication.

Diagnosis

• Stool cultures

• Sometimes rapid stool assay for Shiga toxin

E. coli O157:H7 infection should be distinguished from other infectious diarrheas by isolating the organism from stool cultures. Often, the clinician must specifically ask the laboratory to test for the organism. Because bloody diarrhea and severe abdominal pain without fever suggest various noninfectious etiologies, *E. coli* O157:H7 infection should be considered in suspected cases of ischemic colitis, intussusception, and inflammatory bowel disease. A rapid stool assay for Shiga toxin may help. Patients at risk of noninfectious diarrheas may need sigmoidoscopy. If done, sigmoidoscopy may reveal erythema and edema; barium enema typically shows evidence of edema with thumbprinting.

Treatment

• Supportive care

The mainstay of treatment is supportive. Although *E. coli* is sensitive to most commonly used antibiotics, antibiotics have not been shown to alleviate symptoms, reduce carriage of the organism, or prevent hemolytic-uremic syndrome. Fluoroquinolones are suspected of increasing release of enterotoxins.

In the week after infection, patients at high risk of developing hemolytic-uremic syndrome (eg, children < 5 yr, the elderly) should be observed for early signs, such as proteinuria, hematuria, red cell casts, and rising serum creatinine. Edema and hypertension develop later. Patients who develop complications are likely to require intensive care, including dialysis and other specific therapies, at a tertiary medical center.

Prevention

Correct disposal of the stool of infected people, good hygiene, and careful hand washing with soap limit spread of infection. Preventive measures that may be effective in the day care setting include grouping children known to be infected with *E. coli* O157:H7 or requiring 2 negative stool cultures before allowing infected children to attend. Pasteurization of milk and thorough cooking of beef prevent food-borne transmission.

Reporting outbreaks of bloody diarrhea to public health authorities is important because intervention can prevent additional infections.

Haemophilus Infections

Haemophilus sp cause numerous mild and serious infections, including bacteremia, meningitis, pneumonia, otitis media, cellulitis, and epiglottitis. Diagnosis is by culture and serotyping. Treatment is with antibiotics.

Many *Haemophilus* sp are normal flora in the upper respiratory tract and rarely cause illness. Pathogenic strains enter the upper respiratory tract through droplet inhalation or direct contact. Spread is rapid in nonimmune populations. Children, particularly males, blacks, and Native Americans, are at highest risk of serious infection. Overcrowded living conditions and day care center attendance predispose to infection, as do immunodeficiency states, asplenia, and sickle cell disease.

There are several pathogenic species of *Haemophilus*; the most common is *H. influenzae*, which has 6 distinct encapsulated serotypes (a through f) and numerous nonencapsulated, nontypeable strains. Before the use of *H. influenzae* type b (Hib) conjugate vaccine, most cases of serious, invasive disease were caused by type b.

Diseases caused by *Haemophilus* sp: H. influenzae causes many childhood infections, including meningitis, bacteremia, septic arthritis, pneumonia, tracheobronchitis, otitis media, conjunctivitis, sinusitis, and acute epiglottitis. These infections, as well as endocarditis and UTIs, may occur in adults, although far less commonly. These illnesses are discussed elsewhere in THE MANUAL.

Nontypeable *H. influenzae* strains cause mainly mucosal infections (eg, otitis media, sinusitis, conjunctivitis, bronchitis). Occasionally, nonencapsulated strains cause invasive infections in children, but they may cause up to half of serious *H. influenzae* infections in adults.

H. influenzae biogroup aegyptius (formerly called *H. aegyptius*) may cause mucopurulent conjunctivitis and bacteremic Brazilian purpuric fever. *H. ducreyi* causes chancroid (see p.). *H. parainfluenzae* and *H. aphrophilus* are rare causes of bacteremia, endocarditis, and brain abscess.

Diagnosis

• Cultures

• Sometimes serotyping

Diagnosis is by culture of blood and body fluids. Strains involved in invasive illness should be serotyped.

Treatment

• Various antibiotics depending on site and severity of infection

Treatment depends on nature and location of the infection, but doxycycline, fluoroquinolones, 2nd- and 3rd-generation cephalosporins, and carbapenems are used for invasive disease. The Hib vaccine has markedly reduced the rate of bacteremia. Children with serious illness are hospitalized with contact and respiratory isolation for 24 h after starting antibiotics.

Antibiotic choices depend strongly on the site of infection and require susceptibility testing; many isolates in the US produce β-lactamase. For invasive illness, including meningitis, cefotaxime or ceftriaxone is recommended. For less serious infections, oral cephalosporins, macrolides, and amoxicillin/clavulanate are generally effective. (See individual disease entries for specific recommendations.)

Prevention

Hib conjugate vaccines are available for children ≥ 2 mo of age and have reduced invasive infections (eg, meningitis, epiglottitis, bacteremia) by 99%. A primary series is given at age 2, 4, and 6 mo or at age 2 and 4 mo, depending on the vaccine product. A booster at age 12 to 15 mo is indicated.

Contacts within the household may have asymptomatic *H. influenzae* carriage. Unimmunized or incompletely immunized household contacts < 4 yr are at risk of illness and should receive a dose of

vaccine. In addition, all household members (except pregnant women) should receive prophylaxis with rifampin 600 mg (20 mg/kg for children) po once/day for 4 days. Nursery or day care contacts should receive prophylaxis if ≥ 2 cases of invasive disease occurred in 60 days. The benefit of prophylaxis if only one case occurred has not been established.

HACEK Infections

The HACEK group includes weakly virulent, gram-negative organisms that primarily cause endocarditis.

The HACEK group of nonmotile, gram-negative bacilli or coccobacilli contains a number of minimally pathogenic, slow-growing, fastidious genera. Their primary pathology is endocarditis in susceptible people; about 1% of endocarditis cases are due to this group. The group consists of

• *Haemophilus* sp, which may cause respiratory infections or, less commonly, endocarditis

• *Actinobacillus actinomycetemcomitans*, which usually occurs with *A. israelii* in actinomycosis (see Actinomycosis on p. 1289)

• *Cardiobacterium hominis*

• *Eikenella corrodens*, which usually occurs in human bite wounds, endocarditis, brain and visceral abscesses, osteomyelitis, respiratory infections, uterine infections related to intrauterine devices, and mixed soft-tissue infections

• *Kingella kingae*

Antibiotic sensitivities differ among species, so treatment should be directed by susceptibility testing.

Klebsiella, Enterobacter, and *Serratia* Infections

***Klebsiella, Enterobacter*, and *Serratia* are closely related normal intestinal flora that rarely cause disease in normal hosts.**

Infections with *Klebsiella, Enterobacter*, and *Serratia* are usually hospital-acquired and occur mainly in patients with diminished resistance. Usually, *Klebsiella, Enterobacter*, and *Serratia* cause a wide variety of infections, including bacteremia, surgical site infections, intravascular catheter infections, and respiratory or urinary tract infections that manifest as pneumonia, cystitis, or pyelitis and that may progress to lung abscess, empyema, and septicemia. *Klebsiella* pneumonia, a rare and severe disease with dark brown or red currant-jelly sputum, lung abscess formation, and empyema, is most common among diabetics and alcoholics. *Serratia,* particularly *S. marcescens*, has greater affinity for the urinary tract. *Enterobacter* can cause otitis media, cellulitis, and neonatal sepsis.

Treatment is with 3rd-generation cephalosporins, cefepime, carbapenems, fluoroquinolones, piperacillin/tazobactam, or aminoglycosides. However, because some isolates are resistant to multiple antibiotics, susceptibility testing is essential. *Klebsiella* strains that produce extended-spectrum β-lactamase (ESBL) may develop resistance to cephalosporins during treatment, particularly with ceftazidime. *Enterobacter* strains may be resistant to most β-lactam antibiotics, including 3rd-generation cephalosporins; the β-lactamase enzyme they produce is not inhibited by the usual β-lactamase inhibitors (clavulanate, tazobactam, sulbactam). However, these *Enterobacter* strains may be susceptible to carbapenems (eg, imipenem, meropenem, ertapenem).

Legionella Infections

***Legionella pneumophila* most often causes pneumonia with extrapulmonary features. Diagnosis requires specific growth media, serologic testing, or PCR analysis. Treatment is with doxycycline, macrolides, or fluoroquinolones.**

The first appearance of this organism was in 1976 at a convention of the American Legion—thus, the name Legionnaires' disease. This disease is the pneumonic form of an infection usually caused by *Legionella pneumophila* serogroups 1 through 6. Nonpneumonic infection is called Pontiac fever.

The organisms are often present in soil and freshwater. A building's water supply is often the source of a *Legionella* outbreak. *Legionella* organisms are embedded in a biofilm that forms on the inside of water pipes and containers. The infection is usually acquired by inhaling aerosols of contaminated water (eg, as generated by shower heads, misters, whirlpool baths, or water cooling towers for air-conditioning).

Diseases caused by *Legionella* sp: The lungs are the most common site of infection; community- and hospital-acquired pneumonia may occur.

Extrapulmonary foci of infection occur most frequently in hospitalized patients and most commonly involve the heart. Other sites include the CNS, liver, and intestines. Immunocompromised patients, patients with diabetes mellitus, cigarette smokers, the elderly, and patients with chronic lung disease are principally affected.

Symptoms and Signs

Legionnaires' disease is a flu-like syndrome with acute fever, chills, malaise, myalgias, headache, or confusion. Nausea, loose stools or watery diarrhea, abdominal pain, cough, and arthralgias also frequently occur. Pneumonic manifestations may include dyspnea, pleuritic pain, and hemoptysis.

Mortality is low in otherwise healthy people but can reach 50% in hospital-acquired outbreaks.

Diagnosis

• Direct fluorescent antibody staining

• Sputum culture

• Rapid urinary antigen test (for serogroup 1 only)

Direct fluorescent antibody staining of sputum or lavage fluid is frequently used. In addition, PCR with DNA probing is available. A urinary antigen test is 70% sensitive and 100% specific 3 days after symptom onset but detects only *L. pneumophila* (serogroups 1 through 6) and not non-*pneumophila Legionella*. Paired acute and convalescent antibody assays may yield a delayed diagnosis. A 4-fold increase or an acute titer of ≥ 1:128 is considered diagnostic.

Diagnosis is by culture of sputum or bronchoalveolar lavage fluid; blood cultures are unreliable. Slow growth on laboratory media may delay identification for 3 to 5 days.

Chest x-ray should be done; it usually shows patchy and rapidly asymmetrically progressive infiltrates (even when effective antibiotic therapy is used), with or without small pleural effusions.

Treatment

• Fluoroquinolones

• Doxycycline

A fluoroquinolone given IV or po for 2 to 3 wk is the preferred regimen. Doxycycline is also highly effective. Azithromycin is effective, but erythromycin may be ineffective. Rifampin may be added for severe infections.

Melioidosis

Melioidosis is an infection caused by *Burkholderia* (formerly *Pseudomonas*) *pseudomallei*. Manifestations include pneumonia, septicemia, and localized infection in various organs. Diagnosis is by staining or culture. Treatment with antibiotics, such as ceftazidime, is prolonged.

The organism can be isolated from soil and water and is endemic in Southeast Asia; Australia; Central, West, and East Africa; India; and China. Humans may contract melioidosis by contamination of skin abrasions or burns, ingestion, or inhalation but not directly from infected animals or other humans. In endemic areas, melioidosis is likely to occur in patients with AIDS.

Symptoms and Signs

Infection may be asymptomatic or remain latent for years. Mortality is < 10%, except in acute septicemic melioidosis, which is frequently fatal.

Acute pulmonary infection is the most common form. It varies from mild to overwhelming necrotizing pneumonia. Onset may be abrupt or gradual, with headache, anorexia, pleuritic or dull aching chest pain, and generalized myalgia. Fever is usually > 39° C. Cough, tachypnea, and rales are characteristic. Sputum may be blood-tinged. Chest x-rays usually show upper lobe consolidation, frequently cavitating and resembling TB. Nodular lesions, thin-walled cysts, and pleural effusion may also occur. The WBC count ranges from normal to 20,000/μL.

Disseminated septicemic infection begins abruptly, with septic shock and multiple organ involvement manifested by disorientation, extreme dyspnea, severe headache, pharyngitis, upper abdominal colic, diarrhea, and pustular skin lesions. High fever, hypotension, tachypnea, a bright erythematous flush, and cyanosis are present. Muscle tenderness may be striking. Signs of arthritis or meningitis sometimes occur. Pulmonary signs may be absent or may include rales, rhonchi, and pleural rubs.

Nondisseminated septicemic infection occurs when bacteremia involves only a single organ. It does not usually lead to shock.

Localized (chronic suppurative) infection causes secondary abscesses, most often in the skin, lymph nodes, or bone. Patients may be afebrile. An acute suppurative form is uncommon.

Diagnosis

• Staining and culture

B. pseudomallei can be identified in exudates by methylene blue or Gram stain and by culture. Chest x-rays usually show irregular, nodular (4 to 10 mm) densities. The liver and spleen may be palpable. Liver function tests, AST, and bilirubin are often abnormal. The WBC count is normal or slightly increased.

Treatment

• Sometimes trimethoprim/sulfamethoxazole (TMP/SMX) or ceftazidime

Asymptomatic infection needs no treatment. Mildly ill patients are given TMP/SMX, one double-strength tablet po bid for a minimum of 30 days. Moderately or seriously ill patients are given ceftazidime 30 mg/kg IV q 6 h for 2 to 4 wk (imipenem, meropenem, and piperacillin are acceptable substitutes), then oral TMP/SMX or amoxicillin/clavulanate for 30 to 120 days.

Pertussis

(Whooping Cough)

Pertussis is a highly communicable disease occurring mostly in children and adolescents and caused by *Bordetella pertussis*. Symptoms are initially those of nonspecific URI followed by paroxysmal or spasmodic coughing that usually ends in a prolonged, high-pitched, crowing inspiration (the whoop). Diagnosis is by nasopharyngeal culture, PCR, and serologic assays.

Treatment is with macrolide antibiotics.

Pertussis is endemic throughout the world. Its incidence in the US cycles every 3 to 4 yr. In a given unimmunized locality, it becomes epidemic every 2 to 4 yr. It occurs at all ages, but 71% of cases occur in children < 5 yr, and 38% of cases, including nearly all deaths, occur in infants < 6 mo. Mortality is about 1 to 2% in children < 1 yr and is highest during the first month of life. Most deaths are caused by bronchopneumonia and cerebral complications. It is also serious in the elderly. One attack does not confer life-long natural immunity, but secondary attacks are usually mild and often unrecognized.

Transmission via aerosols of *B. pertussis* (a small, nonmotile, gram-negative coccobacillus) from infected patients, particularly in the catarrhal and early paroxysmal stages, causes disease in 90 to 100% of close contacts. Transmission by contact with contaminated articles is rare. Patients are usually not infectious after the 3rd wk of the paroxysmal phase.

Diseases caused by pertussis: Respiratory complications, including asphyxia in infants, are most common. Otitis media occurs frequently. Bronchopneumonia (common among the elderly) may be fatal at any age. Seizures are common among infants but rare in older children. Hemorrhage into the brain, eyes, skin, and mucous membranes can result from severe paroxysms and consequent anoxia. Cerebral hemorrhage, cerebral edema, and toxic encephalitis may result in spastic paralysis, intellectual disability (mental retardation), or other neurologic disorders. Umbilical herniation and rectal prolapse occasionally occur.

Parapertussis: This disease, caused by *B. parapertussis*, may be clinically indistinguishable from pertussis but is usually milder and less often fatal.

Symptoms and Signs

The incubation period averages 7 to 14 days (maximum 3 wk). *B. pertussis* invades respiratory mucosa, increasing the secretion of mucus, which is initially thin and later viscid and tenacious. Uncomplicated disease lasts about 6 to 10 wk and consists of 3 stages:

• Catarrhal

• Paroxysmal

• Convalescent

The catarrhal stage begins insidiously, generally with sneezing, lacrimation, or other signs of coryza; anorexia; listlessness; and a troublesome, hacking nocturnal cough that gradually becomes diurnal. Hoarseness may occur. Fever is rare.

After 10 to 14 days, the paroxysmal stage begins with an increase in the severity and frequency of the cough. Repeated bouts of ≥ 5 rapidly consecutive forceful coughs occur during a single expiration and are followed by the whoop—a hurried, deep inspiration. Copious viscid mucus may be expelled or bubble from the nares during or after the paroxysms. Vomiting is characteristic. In infants, choking spells (with or without cyanosis) may be more common than whoops.

Symptoms diminish as the convalescent stage begins, usually within 4 wk of onset. Average duration of illness is about 7 wk (range 3 wk to 3 mo). Paroxysmal coughing may recur for months, usually induced in the still sensitive respiratory tract by irritation from a URI.

Diagnosis

• Nasopharyngeal cultures

The catarrhal stage is often difficult to distinguish from bronchitis or influenza. Adenovirus infections and TB should also be considered.

Cultures of nasopharyngeal specimens are positive for *B. pertussis* in 80 to 90% of cases in the catarrhal and early paroxysmal stages. Because special media and prolonged incubation are required, the laboratory should be notified that pertussis is suspected. Specific fluorescent antibody testing of nasopharyngeal smears accurately diagnoses pertussis but is not as sensitive as culture. PCR can also be used. The WBC count is usually between 15,000 and 20,000/μL but may be normal or as high as 60,000/μL, usually with 60 to 80% small lymphocytes.

Parapertussis is differentiated by culture or the fluorescent antibody technique.

Treatment

• Supportive care

• Erythromycin or azithromycin

Hospitalization with respiratory isolation is recommended for seriously ill infants. Isolation is continued until antibiotics have been given for 5 days.

In infants, suction to remove excess mucus from the throat may be lifesaving. O_2 and tracheostomy or nasotracheal intubation is occasionally needed. Expectorants, cough suppressants, and mild sedation are of little value. Because any disturbance can precipitate serious paroxysmal coughing with anoxia, seriously ill infants should be kept in a darkened, quiet room and disturbed as little as possible. Patients treated at home should be quarantined, particularly from susceptible infants, for at least 4 wk from disease onset and until symptoms have subsided.

Antibiotics given during the catarrhal stage may ameliorate the disease. After paroxysms are established, antibiotics usually have no clinical effect but are recommended to limit spread. Preferred drugs are erythromycin 10 to 12.5 mg/kg po q 6 h (maximum 2 g/day) for 14 days or azithromycin 10 to 12 mg/kg po once/day for 5 days. Antibiotics should also be used for bacterial complications (eg, bronchopneumonia, otitis media).

Prevention

Active immunization is part of standard childhood vaccination. Five doses of vaccine are given (usually combined with diphtheria and tetanus [DTP or DTaP]) at age 2, 4, and 6 mo; boosters are given at 15 to 18 mo and 4 to 6 yr. Significant adverse effects from the pertussis component of the vaccine include encephalopathy within 7 days; seizure, with or without fever, within 3 days; persistent, severe, inconsolable screaming or crying for ≥ 3 h; collapse or shock within 48 h; fever ≥ 40.5° C within 48 h; and immediate severe or anaphylactic reaction. These reactions contraindicate further use of pertussis vaccine; combined diphtheria and tetanus vaccine is available without the pertussis component. The acellular vaccine (DTaP) is better tolerated.

Immunity after natural infection lasts about 20 yr. Passive immunization is unreliable and is not recommended.

Close contacts < 7 yr who have had < 4 doses of vaccine should be vaccinated. Contacts of all ages, whether vaccinated or not, should receive a 10-day course of erythromycin 500 mg po qid or 10 to 12.5 mg/kg po qid.

Plague and Other *Yersinia* Infections

(Bubonic Plague; Pestis; Black Death)

Plague is caused by *Yersinia pestis*. Symptoms are either severe pneumonia or massive lymphadenopathy with high fever, often progressing to septicemia. Diagnosis is epidemiologic and clinical, confirmed by culture and serologic testing. Treatment is with streptomycin or doxycycline.

Yersinia (formerly *Pasteurella*) *pestis* is a short bacillus that often shows bipolar staining (especially with Giemsa stain) and may resemble a safety pin.

Plague occurs primarily in wild rodents (eg, rats, mice, squirrels, prairie dogs) and is transmitted from rodent to human by the bite of an infected rat flea vector. Human-to-human transmission occurs by inhaling droplet nuclei from patients with pulmonary infection (primary pneumonic plague), which is highly contagious. In endemic areas in the US, several cases may have been caused by household pets, especially cats. Transmission from cats can be by bite or, if the cat has pneumonic plague, by inhalation of infected droplets.

Massive human epidemics (eg, the Black Death of the Middle Ages) have occurred. More recently, plague has occurred sporadically or in limited outbreaks. In the US, > 90% of human plague occurs in the Southwest, especially New Mexico, Arizona, California, and Colorado. *Yersinia* is considered a possible agent of bioterrorism.

Symptoms and Signs

In **bubonic plague,** the most common form, the incubation period is usually 2 to 5 days but varies from a few hours to 12 days. Onset of fever of 39.5 to 41° C is abrupt, often with chills. The pulse may be rapid and thready; hypotension may occur. Enlarged lymph nodes (buboes) appear with or shortly after the fever. The femoral or inguinal lymph nodes are most commonly involved, followed by axillary, cervical, or multiple nodes. Typically, the nodes are extremely tender and firm, surrounded by considerable edema. They may suppurate in the 2nd wk. The overlying skin is smooth and reddened but often not warm. A primary cutaneous lesion, varying from a small vesicle with slight local lymphangitis to an eschar, occasionally appears at the bite. The patient may be restless, delirious, confused, and uncoordinated. The liver and spleen may be enlarged. Bubonic plague may be complicated by pneumonic plague.

Primary pneumonic plague has a 2- to 3-day incubation period, followed by abrupt onset of high fever, chills, tachycardia, chest pain, and headache, often severe. Cough, not prominent initially, develops within 24 h. Sputum is mucoid at first, rapidly develops blood specks, and then becomes uniformly pink or bright red (resembling raspberry syrup) and foamy. Tachypnea and dyspnea are present, but pleuritic chest pain is not. Signs of consolidation are rare, and rales may be absent.

Septicemic plague may occur with the bubonic form or without the bubonic form (called primary septicemic plague) as an acute, fulminant illness. Abdominal pain, presumably due to mesenteric lymphadenopathy, occurs in 40% of patients. Disseminated intravascular coagulopathy, gangrene of the extremities (hence, the name Black Death), and multiorgan failure eventually develop. Pharyngeal plague and plague meningitis are less common forms.

Pestis minor, a more benign form of bubonic plague, usually occurs only in endemic areas. Lymphadenitis, fever, headache, and prostration subside within a week.

The mortality rate for untreated patients with bubonic plague is about 60%; most deaths result from septicemia in 3 to 5 days. Most untreated patients with pneumonic plague die within 48 h of symptom onset. Septicemic plague may be fatal before bubonic or pulmonary manifestations predominate.

Diagnosis

• Staining, cultures, and serologic testing

Diagnosis is made by stain and culture of the organism, typically by needle aspiration of a bubo (surgical drainage may disseminate the organism); blood and sputum cultures should also be obtained. Other tests include immunofluorescent staining and serology; a titer of > 1:16 or a 4-fold rise between acute and convalescent titers is positive. PCR testing, if available, is diagnostic. Prior vaccination does not exclude plague; clinical illness may occur in vaccinated people.

Patients with pulmonary symptoms or signs should have a chest x-ray, which shows a rapidly progressing pneumonia in pneumonic plague. The WBC count is usually 10,000 to 20,000/μL with numerous immature

neutrophils.

Treatment

• Streptomycin

• Alternatively, doxycycline, gentamicin, or chloramphenicol

Immediate treatment reduces mortality to < 5%. In septicemic or pneumonic plague, treatment must begin within 24 h with streptomycin 15 mg/kg (up to 1 g) IM bid for 10 days or until 3 days after temperature has returned to normal. Doxycycline 100 mg IV or po q 12 h is an alternative. Gentamicin and chloramphenicol are also effective.

Chloramphenicol is preferred for patients with infection of tissue spaces into which other drugs pass poorly (eg, plague meningitis, endophthalmitis). Chloramphenicol should be given in a loading dose of 25 mg/kg IV, followed by 12.5 mg/kg IV or po q 6 h.

Routine isolation precautions are adequate for patients with bubonic plague. Those with primary or secondary pneumonic plague require strict respiratory isolation.

Prevention

All pneumonic plague contacts should be under medical surveillance. Temperature should be taken q 4 h for 6 days. They and others in close contact with plague patients or with contaminated fluids or tissue should receive prophylaxis with doxycycline 100 mg po q 12 h (for children < 8 yr, trimethoprim/sulfamethoxazole [TMP/SMX] 20 mg/kg [of the SMX component] q 12 h). Travelers should be given prophylaxis with doxycycline 100 mg po q 12 h during exposure periods. Plague vaccine is available but is recommended mainly for laboratory workers and researchers because immunity requires about 1 mo to develop.

Rodents should be controlled and repellents used to minimize flea bites.

Other *Yersinia* Infections

Yersinia enterocolitica and *Y. pseudotuberculosis* are zoonoses acquired by ingestion of contaminated food or water; they occur worldwide.

Y. enterocolitica is a common cause of diarrheal disease and mesenteric adenitis that clinically mimics appendicitis. *Y. pseudotuberculosis* most commonly causes mesenteric adenitis and has been suspected in cases of interstitial nephritis, hemolytic-uremic syndrome, and a scarlet fever-like illness. Both species can cause pharyngitis, septicemia, focal infections in multiple organs, postinfectious erythema nodosum, and reactive arthritis. In patients with chronic liver disease or iron overload, mortality from septicemia may be as high as 50%, even with treatment.

The organisms can be identified in standard cultures from normally sterile sites. Selective culture methods are required for nonsterile specimens. Serologic assays are available but difficult and not standardized. Diagnosis, particularly of reactive arthritis, requires a high index of suspicion and close communication with the clinical laboratory.

Treatment of diarrhea is supportive because the disease is self-limited. Septic complications require β-lactamase-resistant antibiotics guided by susceptibility testing.

Prevention focuses on food handling and preparation, household pets, and epidemiology of suspected outbreaks.

Proteeae Infections

The Proteeae are normal fecal flora that often cause infection in patients whose normal flora

have been disturbed by antibiotic therapy.

The Proteeae constitute at least 3 genera of gram-negative organisms:

• *Proteus: P. mirabilis, P. vulgaris*, and *P. myxofaciens*

• *Morganella: M. morganii*

• *Providencia: P. rettgeri, P. alcalifaciens*, and *P. stuartii*

However, *P. mirabilis* causes most human infections. These organisms are normal fecal flora and are present in soil and water. They are often present in superficial wounds, draining ears, and sputum, particularly in patients whose normal flora has been eradicated by antibiotic therapy. They may cause bacteremia and deep-seated infections, particularly in the ears and mastoid sinuses, peritoneal cavity, and urinary tract of patients with chronic UTIs or with renal or bladder stones.

P. mirabilis is often sensitive to ampicillin, carbenicillin, ticarcillin, piperacillin, cephalosporins, and aminoglycosides and resistant to tetracyclines. Multidrug-resistant *P. mirabilis* is an emerging problem. Indole-positive species (*P. vulgaris, M. morganii, P. rettgeri*) tend to be more resistant but generally are sensitive to fluoroquinolones, carbapenems, piperacillin/tazobactam, 3rd-generation cephalosporins, and cefixime.

Pseudomonas and Related Infections

Pseudomonas aeruginosa and other members of this group of gram-negative bacilli are opportunistic pathogens that frequently cause hospital-acquired infections, particularly in ventilator patients, burn patients, and patients with chronic debility. Many sites can be infected, and infection is usually severe. Diagnosis is by culture. Antibiotic choice varies with the pathogen and must be guided by susceptibility testing because resistance is common.

Epidemiology

Pseudomonas is ubiquitous and favors moist environments. In humans, *P. aeruginosa* is the most common pathogen, but infection may result from *P. paucimobilis, P. putida, P. fluorescens*, or *P. acidovorans*. Other important hospital-acquired pathogens formerly classified as *Pseudomonas* include *Burkholderia cepacia* and *Stenotrophomonas maltophilia. B. pseudomallei* causes a distinct disease known as melioidosis that is limited mostly to the Asian tropics (see p.).

P. aeruginosa is present occasionally in the axilla and anogenital areas of normal skin but rarely in stool unless antibiotics are being given. In hospitals, the organism is frequently present in sinks, antiseptic solutions, and urine receptacles. Transmission to patients by health care practitioners may occur, especially in burn and neonatal ICUs, unless infection control practices are meticulously followed.

Diseases Caused by *Pseudomonas*

Most *P. aeruginosa* infections occur in hospitalized patients, particularly those who are debilitated or immunocompromised. *P. aeruginosa* is a common cause of infections in ICUs. HIV-infected patients, particularly those in advanced stages, are at risk of community-acquired *P. aeruginosa* infections.

Pseudomonas infections can develop in many anatomic sites, including skin, subcutaneous tissue, bone, ears, eyes, urinary tract, and heart valves. The site varies with the portal of entry and the patient's vulnerability. In hospitalized patients, the first sign may be overwhelming gram-negative sepsis.

Skin and soft-tissue infections: In burns, the region below the eschar can become heavily infiltrated with organisms, serving as a focus for subsequent bacteremia—an often lethal complication.

Deep puncture wounds of the foot are often infected by *P. aeruginosa*. Draining sinuses, cellulitis, and

osteomyelitis may result. Drainage from puncture wounds often has a sweet, fruity smell.

Folliculitis acquired in hot tubs is often caused by *P. aeruginosa*.

External otitis, common in tropical climates, is the most common form of *Pseudomonas* infection involving the ear. A more severe form, referred to as malignant external otitis (see p.), can develop in diabetic patients. It is manifested by severe ear pain, often with unilateral cranial nerve palsies, and requires parenteral therapy.

Ecthyma gangrenosum is a skin lesion that occurs in neutropenic patients and is usually caused by *P. aeruginosa*. It is characterized by erythematous, centrally ulcerated, purpleblack areas about 1 cm in diameter occurring most often in the axillary, inguinal, or anogenital areas.

Respiratory tract infections: *P. aeruginosa* is a frequent cause of ventilator-associated pneumonia. In HIV-infected patients, *Pseudomonas* most commonly causes pneumonia or sinusitis. *Pseudomonas* bronchitis is common late in the course of cystic fibrosis. Isolates from patients with cystic fibrosis have a characteristic mucoid colonial morphology.

Other infections: *Pseudomonas* is a common cause of nosocomial UTI, especially in patients who have had urologic manipulation or obstructive uropathy. *Pseudomonas* commonly colonizes the urinary tract in catheterized patients, especially those who have received broad-spectrum antibiotics.

Ocular involvement generally manifests as corneal ulceration, most often after trauma, but contamination of contact lenses or lens fluid has been implicated in some cases.

Rarely, *Pseudomonas* causes acute bacterial endocarditis, usually on prosthetic valves in patients who have had open-heart surgery or on natural valves in IV drug abusers.

Bacteremia: Many *Pseudomonas* infections can cause bacteremia. In nonintubated patients without a detectable urinary focus, especially if infection is due to a species other than *P. aeruginosa*, bacteremia suggests contaminated IV fluids, drugs, or antiseptics used in placing the IV catheter.

Diagnosis

• Culture

Diagnosis depends on culturing the organism from the site of infection: blood, skin lesions, drainage fluid, urine, CSF, or eye. Localized infection may produce a fruity smell, and pus may be greenish.

Treatment

• Various antibiotics depending on site and severity of infection and susceptibility testing

Localized infection: Hot-tub folliculitis resolves spontaneously and does not require antibiotic therapy.

External otitis is treated with 1% acetic acid irrigations or topical drugs such as polymyxin B or colistin. More severe infection is treated with fluoroquinolones.

Focal soft-tissue infection may require early surgical debridement of necrotic tissue and drainage of abscesses in addition to antibiotics.

Small corneal ulcers are treated with ciprofloxacin 0.3% or levofloxacin 0.5%. Fortified (higher than stock concentration) antibiotic drops, such as tobramycin 15 mg/mL, are used for more significant ulcers. Frequent dosing (eg, q 1 h around the clock) is necessary initially. Eye patching is contraindicated because it produces a dark warm environment that favors bacterial growth and prevents administration of topical drugs.

Asymptomatic bacteriuria is not treated with antibiotics, except during pregnancy and before urologic manipulation. Patients with symptomatic UTIs can often be treated with levofloxacin 500 mg po once/day or ciprofloxacin 400 mg po bid.

Systemic infection: Parenteral therapy is required, typically with an aminoglycoside plus an antipseudomonal β-lactam, an anti-pseudomonal cephalosporin (eg, cefepime, cefoperazone), or the carbapenems meropenem or imipenem.

Right-sided endocarditis can be treated with antibiotics, but usually the infected valve must be removed to cure an infection involving the mitral, aortic, or prosthetic valve.

In neutropenic patients with marginal renal function, nonaminoglycoside combinations, such as double β-lactams or a β-lactam plus a fluoroquinolone, are also satisfactory.

P. aeruginosa resistance may occur among patients treated with ceftazidime, ciprofloxacin, gentamicin, meropenem, or imipenem.

Salmonella Infections

The 2200 known serotypes of *Salmonella* may be grouped into

• Those highly adapted to human hosts: This group includes *S. typhi* and *S. paratyphi* types A, B (also called *S. schottmulleri*), and C (also called *S. hirschfeldii*), which are pathogenic only in humans and commonly cause enteric (typhoid) fever.

• Those adapted to nonhuman hosts or causing disease almost exclusively in animals. Two strains within this group, *S. dublin* and *S. choleraesuis*, also cause disease in humans.

• Those unadapted to specific hosts: This group, designated *S. enteritidis*, includes > 2000 serotypes that cause gastroenteritis and accounts for 85% of all *Salmonella* infections in the US.

Typhoid Fever

Typhoid fever is a systemic disease caused by *Salmonella typhi*. Symptoms are high fever, prostration, abdominal pain, and a rose-colored rash. Diagnosis is clinical and confirmed by culture. Treatment is with ceftriaxone or ciprofloxacin.

Epidemiology

About 400 to 500 cases of typhoid fever are reported annually in the US, mainly among US travelers returning from endemic regions. Typhoid bacilli are shed in stool of asymptomatic carriers or in stool or urine of people with active disease. Inadequate hygiene after defecation may spread *S. typhi* to community food or water supplies. In endemic areas where sanitary measures are generally inadequate, *S. typhi* is transmitted more frequently by water than by food. In developed countries, transmission is chiefly by food that has been contaminated during preparation by healthy carriers. Flies may spread the organism from feces to food. Occasional transmission by direct contact (fecal-oral route) may occur in children during play and in adults during sexual practices. Rarely, hospital personnel who have not taken adequate enteric precautions have acquired the disease when changing soiled bedclothes.

The organism enters the body via the GI tract and gains access to the bloodstream via the lymphatic channels. Intestinal ulceration, hemorrhage, and perforation may occur in severe cases.

Carrier state: About 3% of untreated patients, referred to as chronic enteric carriers, harbor organisms in their gallbladder and shed them in stool for > 1 yr. Some carriers have no history of clinical illness. Most of the estimated 2000 carriers in the US are elderly women with chronic biliary disease. Obstructive uropathy related to schistosomiasis may predispose certain typhoid patients to urinary carriage. Epidemiologic data indicate that typhoid carriers are more likely than the general population to develop hepatobiliary cancer.

Symptoms and Signs

The incubation period (usually 8 to 14 days) is inversely related to the number of organisms ingested. Onset is usually gradual, with fever, headache, arthralgia, pharyngitis, constipation, anorexia, and abdominal pain and tenderness. Less common symptoms include dysuria, nonproductive cough, and epistaxis.

Without treatment, the temperature rises in steps over 2 to 3 days, remains elevated (usually 39.4 to 40°C) for another 10 to 14 days, begins to fall gradually at the end of the 3rd wk, and reaches normal levels during the 4th wk. Prolonged fever is often accompanied by relative bradycardia and prostration. CNS symptoms such as delirium, stupor, or coma occur in severe cases. In about 10% of patients, discrete pink, blanching lesions (rose spots) appear in crops on the chest and abdomen during the 2nd wk and resolve in 2 to 5 days. Splenomegaly, leukopenia, anemia, liver function abnormalities, proteinuria, and a mild consumption coagulopathy are common. Acute cholecystitis and hepatitis may occur.

Late in the disease, when intestinal lesions are most prominent, florid diarrhea may occur, and the stool may contain blood (occult in 20% of patients, gross in 10%). In about 2% of patients, severe bleeding occurs during the 3rd wk, with a mortality rate of about 25%. An acute abdomen and leukocytosis during the 3rd wk may suggest intestinal perforation, which usually involves the distal ileum and occurs in 1 to 2% of patients. Pneumonia may develop during the 2nd or 3rd wk and may be due to secondary pneumococcal infection, although *S. typhi* can also cause pulmonary infiltrates. Bacteremia occasionally leads to focal infections such as osteomyelitis, endocarditis, meningitis, soft-tissue abscesses, glomerulitis, or GU tract involvement. Atypical presentations, such as pneumonitis, fever only, or, very rarely, symptoms consistent with UTI, may delay diagnosis. Convalescence may last several months.

In 8 to 10% of untreated patients, symptoms and signs similar to the initial clinical syndrome recur about 2 wk after defervescence. For unclear reasons, antibiotic therapy during the initial illness increases the incidence of febrile relapse to 15 to 20%. If antibiotics are restarted at the time of relapse, the fever abates rapidly, unlike the slow defervescence that occurs during the primary illness. Occasionally, a 2nd relapse occurs.

Diagnosis

• Cultures

Other infections causing a similar presentation include other *Salmonella* infections, the major rickettsioses, leptospirosis, disseminated TB, malaria, brucellosis, tularemia, infectious hepatitis, psittacosis, *Yersinia enterocolitica* infection, and lymphoma. Early in its clinical course, typhoid fever may resemble malaria.

Cultures of blood, stool, and urine should be obtained. Blood cultures are usually positive only during the first 2 wk of illness, but stool cultures are usually positive during the 3rd to 5th wk. If these cultures are negative and typhoid fever is strongly suspected, culture from a bone marrow biopsy specimen may reveal the organism.

Typhoid bacilli contain antigens (O and H) that stimulate the host to form corresponding antibodies. A 4-fold rise in O and H antibody titers in paired specimens obtained 2 wk apart suggests *S. typhi* infection. However, this test is only moderately (70%) sensitive and lacks specificity; many nontyphoidal *Salmonella* strains cross-react, and liver cirrhosis causes false-positives.

Prognosis

Without antibiotics, the mortality rate is about 12%. With prompt therapy, the mortality rate is 1%. Most deaths occur in malnourished people, infants, and the elderly. Stupor, coma, or shock reflects severe disease and a poor prognosis. Complications occur mainly in patients who are untreated or in whom treatment is delayed.

Treatment

• Ceftriaxone

• Sometimes a fluoroquinolone

Preferred antibiotics include ceftriaxone 1 g IM or IV q 12 h (25 to 37.5 mg/kg in children) for 14 days and various fluoroquinolones (eg, ciprofloxacin 500 mg po bid for 10 to 14 days, levofloxacin 500 mg po or IV once/day for 14 days, moxifloxacin 400 mg po or IV once/day for 14 days). Chloramphenicol 500 mg po or IV q 6 h is still widely used, but resistance is increasing. Fluoroquinolones may be used in children. Alternative therapies, depending on in vitro sensitivity, include amoxicillin 25 mg/kg po qid, trimethoprim/sulfamethoxazole (TMP/SMX) 320/1600 bid or 10 mg/kg (of the TMP component) bid, and azithromycin 1 g po on day 1, then 500 mg once/day for 6 days.

Corticosteroids may be added to antibiotics to treat severe toxicity. Defervescence and clinical improvement usually follow. Prednisone 20 to 40 mg once/day po (or equivalent) for the first 3 days of treatment usually suffices. Higher doses of corticosteroids (dexamethasone 3 mg/kg IV initially, followed by 1 mg/kg q 6 h for 48 h total), are used in patients with marked delirium, coma, or shock.

Nutrition should be maintained with frequent feedings. While febrile, patients are usually kept on bed rest. Salicylates (which may cause hypothermia and hypotension), as well as laxatives and enemas, should be avoided. Diarrhea may be minimized with a clear liquid diet; parenteral nutrition may be needed temporarily. Fluid and electrolyte therapy and blood replacement may be needed.

Intestinal perforation and associated peritonitis call for surgical intervention and broader gram-negative and anti-*Bacteroides fragilis* coverage.

Relapses are treated the same as the initial illness, although duration of antibiotic therapy seldom needs to be > 5 days.

Patients must be reported to the local health department and prohibited from handling food until proven free of the organism. Typhoid bacilli may be isolated for as long as 3 to 6 mo after the acute illness in people who do not become carriers. Thereafter, 3 stool cultures at weekly intervals must be negative to exclude a carrier state.

Carriers: Carriers with normal biliary tracts should be given antibiotics. The cure rate is about 60% with amoxicillin 2 g po tid for 4 wk.

In some carriers with gallbladder disease, eradication has been achieved with TMP/SMX and rifampin. In other cases, cholecystectomy with 1 to 2 days of preoperative antibiotics and 2 to 3 days of postoperative antibiotics is effective.

Prevention

Drinking water should be purified, sewage should be disposed of effectively, milk should be pasteurized, chronic carriers should avoid handling food, and adequate patient isolation precautions should be implemented. Special attention to enteric precautions is important. Travelers in endemic areas should avoid ingesting raw leafy vegetables, other foods stored or served at room temperature, and untreated water. Unless water is known to be safe, it should be boiled or chlorinated before drinking.

A live-attenuated oral typhoid vaccine is available (Ty21a strain) and is about 70% effective. It is given every other day for a total of 4 doses. Because the vaccine contains living *S. typhi* organisms, it is contraindicated in patients who are immunosuppressed. In the US, the Ty21a vaccine is not used in children < 6 yr. An alternative is the single-dose, IM Vi polysaccharide vaccine, which is 64 to 72% effective and is well tolerated, but it is not used in children < 2 yr.

Nontyphoidal *Salmonella* Infections

Nontyphoidal salmonellae, mainly *Salmonella enteritidis*, primarily cause gastroenteritis, bacteremia, and focal infection. Symptoms may be diarrhea, high fever with prostration, or symptoms of focal infection. Diagnosis is by cultures of blood, stool, or site specimens. Treatment, when indicated, is with trimethoprim/sulfamethoxazole or ciprofloxacin, with surgery for abscesses, vascular lesions, and bone and joint infections.

Most nontyphoidal *Salmonella* infections are caused by *S. enteritidis*. These infections are common and remain a significant public health problem in the US. Many serotypes of *S. enteritidis* have been given names and are referred to informally as if they were separate species even though they are not. The most common *Salmonella* serotypes in the US include *S. typhimurium, S. heidelberg, S. newport, S. infantis, S. agona, S. montevideo*, and *S. saint-paul.*

Human disease occurs by direct and indirect contact with numerous species of infected animals, the foodstuffs derived from them, and their excreta. Infected meat, poultry, raw milk, eggs, and egg products are common sources of *Salmonella*. Other reported sources include infected pet turtles and reptiles, carmine red dye, and contaminated marijuana.

Risk factors: Subtotal gastrectomy, achlorhydria (or ingestion of antacids), sickle cell anemia, splenectomy, louse-borne relapsing fever, malaria, bartonellosis, cirrhosis, leukemia, lymphoma, and HIV infection are all risk factors for *Salmonella* infection.

Diseases caused by nontyphoidal *Salmonella* sp: Each *Salmonella* serotype can cause any or all of the clinical syndromes described below, although given serotypes tend to produce specific syndromes. Enteric fever, for instance, is caused by *S. paratyphi* types A, B, and C.

An asymptomatic carrier state may also occur. However, carriers do not appear to play a major role in large outbreaks of nontyphoidal gastroenteritis. Persistent shedding of organisms in the stool for ≥ 1 yr occurs in only 0.2 to 0.6% of patients with nontyphoidal *Salmonella* infections.

Symptoms and Signs

Salmonella infection may manifest as

• Gastroenteritis

• Enteric fever

• Bacteremia

• Focal disease

Gastroenteritis usually starts 12 to 48 h after ingestion of organisms, with nausea and cramping abdominal pain followed by diarrhea, fever, and sometimes vomiting. Usually, the stool is watery but may be a pastelike semisolid. Rarely, mucus or blood is present. The disease is usually mild, lasting 1 to 4 days. Occasionally, a more severe, protracted illness occurs.

Enteric fever in a less severe form than typhoid is characterized by fever, prostration, and septicemia.

Bacteremia is relatively uncommon in patients with gastroenteritis. However, *S. choleraesuis, S. typhimurium*, and *S. heidelberg*, among others, can cause a sustained and frequently lethal bacteremic syndrome lasting ≥ 1 wk, with prolonged fever, headache, malaise, and chills but rarely diarrhea. Patients may have recurrent episodes of bacteremia or other invasive infections (eg, septic arthritis) due to *Salmonella*. Multiple *Salmonella* infections in a patient without other risk factors should prompt HIV testing.

Focal *Salmonella* infection can occur with or without sustained bacteremia, causing pain in or referred

from the involved organ—the GI tract (liver, gallbladder, appendix), endothelial surfaces (eg, atherosclerotic plaques, ileofemoral or aortic aneurysms, heart valves), pericardium, meninges, lungs, joints, bones, GU tract, or soft tissues. Preexisting solid tumors are occasionally seeded and develop abscesses that may, in turn, become a source of *Salmonella* bacteremia. *S. choleraesuis* and *S. typhimurium* are the most common causes of focal infection.

Diagnosis

• Cultures

Diagnosis is by isolating the organism from stool or another infected site. In bacteremic and focal forms, blood cultures are positive, but stool cultures are generally negative. In stool specimens stained with methylene blue, WBCs are often seen, indicating inflammatory colitis.

Treatment

• Supportive care

• Ciprofloxacin or trimethoprim/sulfamethoxazole (TMP/SMX) only for high-risk patients and patients with systemic or focal infections

Gastroenteritis is treated symptomatically with oral or IV fluids (see p. 149). Antibiotics do not hasten resolution, may prolong excretion of the organism, and are unwarranted in uncomplicated cases. However, in elderly nursing home residents, infants, and patients with HIV infection, increased mortality dictates treatment with antibiotics. Antibiotic resistance is more common with nontyphoidal *Salmonella* than with *S. typhi*. TMP/SMX 5 mg/kg (of the TMP component) po q 12 h for children and ciprofloxacin 500 mg po q 12 h for adults are acceptable regimens. Nonimmunocompromised patients should be treated for 3 to 5 days; patients with AIDS may require prolonged suppression to prevent relapses. Systemic or focal disease should be treated with antibiotic doses as outlined above for typhoid fever. Sustained bacteremia is generally treated for 4 to 6 wk. Abscesses should be drained surgically. At least 4 wk of antibiotic therapy should follow surgery. Infected aneurysms and heart valves and bone or joint infections usually require surgical intervention and prolonged courses of antibiotics. The prognosis is usually good, unless severe underlying disease is present.

Carriers: Asymptomatic carriage is usually self-limited, and antibiotic treatment is rarely required. In unusual cases (eg, in food handlers or health care workers), eradication may be attempted with ciprofloxacin 500 mg po q 12 h for 1 mo. Follow-up stool cultures should be obtained in the weeks after drug administration to document elimination of *Salmonella*.

Prevention

Preventing contamination of foodstuffs by infected animals and humans is paramount. Preventive measures for travelers discussed on p. 1261 also apply to most other enteric infections. Case reporting is essential.

Shigellosis

(Bacillary Dysentery)

Shigellosis is an acute infection of the intestine caused by *Shigella* sp. Symptoms include fever, nausea, vomiting, and diarrhea that is usually bloody. Diagnosis is clinical and confirmed by stool culture. Treatment is supportive, mostly with rehydration; antibiotics (eg, ampicillin, trimethoprim/sulfamethoxazole) are optional.

The genus *Shigella* is distributed worldwide and is the typical cause of inflammatory dysentery, responsible for 5 to 10% of diarrheal illness in many areas. *Shigella* is divided into 4 major subgroups: A, B, C, and D, which are subdivided into serologically determined types. *S. flexneri* and *S. sonnei* are more widespread than *S. boydii* and the particularly virulent *S. dysenteriae. S. sonnei* is the most common

isolate in the US.

The source of infection is the feces of infected people or convalescent carriers. Direct spread is by the fecal-oral route. Indirect spread is by contaminated food and fomites. Flies serve as vectors. Epidemics occur most frequently in overcrowded populations with inadequate sanitation. Shigellosis is particularly common among younger children living in endemic areas. Adults usually have less severe disease.

Convalescents and subclinical carriers may be significant sources of infection, but true long-term carriers are rare. Infection imparts little or no immunity.

Shigella organisms penetrate the mucosa of the colon, causing mucus secretion, hyperemia, leukocytic infiltration, edema, and often superficial mucosal ulcerations. *Shigella dysenteriae* type 1 (not commonly present in the US, except in travelers returning from endemic areas) produces Shiga toxin, which causes marked watery diarrhea and sometimes hemolytic-uremic syndrome.

Symptoms and Signs

The incubation period is 1 to 4 days. The most common presentation, watery diarrhea, is indistinguishable from other bacterial, viral, and protozoan infections that induce secretory activity of intestinal epithelial cells.

In adults, initial symptoms may be episodes of gripping abdominal pain, urgency to defecate, and passage of formed feces that temporarily relieves the pain. These episodes recur with increasing severity and frequency. Diarrhea becomes marked, with soft or liquid stools containing mucus, pus, and often blood. Rectal prolapse and consequent fecal incontinence may result from severe tenesmus. However, adults may present without fever, with nonbloody and nonmucoid diarrhea, and with little or no tenesmus. The disease usually resolves spontaneously in adults—mild cases in 4 to 8 days, severe cases in 3 to 6 wk. Significant dehydration and electrolyte loss with circulatory collapse and death occur mainly in debilitated adults and children < 2 yr.

Rarely, shigellosis starts suddenly with ricewater or serous (occasionally bloody) stools. The patient may vomit and rapidly become dehydrated. Infection may manifest as delirium, seizures, and coma but with little or no diarrhea. Death may occur in 12 to 24 h.

In young children, onset is sudden, with fever, irritability or drowsiness, anorexia, nausea or vomiting, diarrhea, abdominal pain and distention, and tenesmus. Within 3 days, blood, pus, and mucus appear in the stools. The number of stools may increase to ≥ 20/day, and weight loss and dehydration become severe. If untreated, children may die in the first 12 days. If children survive, acute symptoms subside by the 2nd wk.

Complications: The hemolytic-uremic syndrome may complicate shigellosis due to *S. dysenteriae* type 1 in children. Secondary bacterial infections may occur, especially in debilitated and dehydrated patients. Severe mucosal ulcerations may cause significant acute blood loss. Patients (particularly those with the HLA-B27 genotype) may develop reactive arthritis (arthritis, conjunctivitis, urethritis) after shigellosis (and other enteritides).

Other complications are uncommon but include seizures in children, myocarditis, and, rarely, intestinal perforation. Infection does not become chronic and is not an etiologic factor in ulcerative colitis.

Diagnosis

• Stool cultures

Diagnosis is facilitated by a high index of suspicion during outbreaks and in endemic areas and by the presence of fecal leukocytes on smears stained with methylene blue or Wright's stain. Stool cultures are diagnostic and should be obtained. In patients with symptoms of dysentery (bloody and mucoid stools), the differential diagnosis should include invasive *Escherichia coli, Salmonella, Yersinia,* and *Campylobacter* infections; amebiasis; and viral diarrheas.

The mucosal surface, as seen through a proctoscope, is diffusely erythematous with numerous small ulcers. Although leukopenia or marked leukocytosis may be present, it averages 13,000/μL. Hemoconcentration is common, as is diarrhea-induced metabolic acidosis.

Treatment

• Supportive care

• For severely ill or at-risk patients, a fluoroquinolone or trimethoprim/sulfamethoxazole (TMP/SMX)

Fluid loss is treated symptomatically with oral or IV fluids (see p.). Antibiotics can reduce the symptoms and shedding of *Shigella* but are not necessary for healthy adults with mild illness. However, certain patients, including the following, should usually be treated:

• Children

• The elderly

• Debilitated patients

• Patients with severe disease

For adults, a fluoroquinolone, such as ciprofloxacin 500 mg po q 12 h for 3 to 5 days, or TMP/SMX one double-strength tablet q 12 h is the treatment of choice. For children, treatment is TMP/SMX 4 mg/kg (of the TMP component) po q 12 h. Many *Shigella* isolates are likely to be resistant to ampicillin and tetracycline.

Prevention

Hands should be washed thoroughly before handling food, and soiled garments and bedclothes should be immersed in covered buckets of soap and water until they can be boiled. Appropriate isolation techniques (especially stool isolation) should be used with patients and carriers.

A live oral vaccine is being developed, and field trials in endemic areas hold promise. However, immunity is generally type specific.

Tularemia

(Rabbit or Deer Fly Fever)

Tularemia is a febrile disease caused by *Francisella tularensis*; it may resemble typhoid fever. Symptoms are a primary local ulcerative lesion, regional lymphadenopathy, profound systemic symptoms, and, occasionally, atypical pneumonia. Diagnosis is primarily epidemiologic and clinical and supported by serologic tests. Treatment is with streptomycin, gentamicin, chloramphenicol, or doxycycline.

There are 7 clinical syndromes associated with tularemia (see Table 135-2). The causative organism, *F. tularensis*, is a small, pleomorphic, nonmotile, nonsporulating aerobic bacillus that enters the body by

• Ingestion of contaminated food or water

• Bite of an infected arthropod vector (ticks, deer flies, fleas)

• Inhalation

• Direct contact with infected tissues or material

The organism can penetrate apparently unbroken skin but may actually enter through microlesions.

There are 2 types of *F. tularensis*: type A and type B. Type A, a more virulent serotype for humans, usually occurs in rabbits and rodents in the US and Canada. Type B usually causes a mild ulceroglandular infection and occurs in water and aquatic animals in Europe and Asia.

Hunters, butchers, farmers, and fur handlers are most commonly infected. In winter months, most cases result from contact (especially during skinning) with infected wild rabbits. In summer months, infection usually follows handling of other infected animals or birds or bites of infected ticks or other arthropods. Rarely, cases result from eating undercooked infected meat, drinking contaminated water, or mowing fields in endemic areas. In the Western states, ticks, deer flies, horse flies, and direct contact with infected animals are other sources of infection. Human-to-human transmission has not been reported. Laboratory workers are at particular risk because infection is readily acquired during normal handling of infected specimens. Tularemia is considered a possible agent of bioterrorism.

In disseminated cases, characteristic focal necrotic lesions in various stages of evolution are scattered throughout the body. They are 1 mm to 8 cm and whitish yellow; they are seen externally as the primary lesions on the fingers, eyes, or mouth and commonly occur in lymph nodes, spleen, liver, kidneys, and lungs. In pneumonia, necrotic foci occur in the lungs. Although severe systemic toxicity may occur, no toxins have been demonstrated.

Symptoms and Signs

Onset occurs suddenly, 1 to 10 (usually 2 to 4) days after exposure, with headache, chills,

[**Table 135-2.** Types of Tularemia*]

nausea, vomiting, fever of 39.5° to 40° C, and severe prostration. Extreme weakness, recurring chills, and drenching sweats develop. Clinical manifestations depend to some extent on the type of exposure (see Table 135-2).

Within 24 to 48 h, an inflamed papule appears at the site of exposure (finger, arm, eye, roof of the mouth), except in glandular or typhoidal tularemia. The papule rapidly becomes pustular and ulcerates, producing a clean ulcer crater with a scanty, thin, colorless exudate. Ulcers are usually single on the extremities but multiple in the mouth or eyes. Usually, only one eye is affected. Regional lymph nodes enlarge and may suppurate and drain profusely. A typhoid-like state frequently develops by the 5th day, and the patient may develop atypical pneumonia, sometimes accompanied by delirium.

Pneumonic tularemia can occur after inhalation or by hematogenous spread from another type of tularemia; it develops in 10 to 15% of ulceroglandular tularemia cases and in about 50% of typhoidal tularemia cases. Although signs of consolidation are frequently present, reduced breath sounds and occasional rales may be the only physical findings in tularemic pneumonia. A dry, nonproductive cough is associated with a retrosternal burning sensation. A nonspecific roseola-like rash may appear at any stage of the disease. Splenomegaly and perisplenitis may occur. In untreated cases, temperature remains elevated for 3 to 4 wk and resolves gradually. Mediastinitis, lung abscess, and meningitis are rare complications.

Mortality is almost nil in treated cases and about 6% in untreated cases of ulceroglandular tularemia. Mortality rates are higher for type A infection and for typhoidal, septicemic, and pneumonic tularemia; they are as high as 33% for untreated cases. Death usually results from overwhelming infection, pneumonia, meningitis, or peritonitis. Relapses can occur in inadequately treated cases. One attack confers immunity.

Diagnosis

• Cultures

• Acute and convalescent serologic testing

Diagnosis is suspected based on a history of contact with rabbits or wild rodents or exposure to arthropod vectors, the sudden onset of symptoms, and the characteristic primary lesion.

Patients should have cultures of blood and relevant clinical material (eg, sputum, lesions); routine cultures may be negative, and the laboratory should be notified that tularemia is suspected so that appropriate media can be used (and appropriate safety precautions ensured). Acute and convalescent antibody titers should be done 2 wk apart. A 4-fold rise or a single titer > 1:128 is diagnostic. The serum of patients with brucellosis may cross-react to *F. tularensis* antigens but usually in much lower titers. Fluorescent antibody staining is used by some laboratories. Leukocytosis is common, but the WBC count may be normal with an increase only in the proportion of PMNs.

Because this organism is highly infectious, samples and culture media suspected of tularemia should be handled with extreme caution and, if possible, processed by a high-level biosafety containment-equipped laboratory with a level 3 rating.

Treatment

• Streptomycin (plus chloramphenicol for meningitis)

The preferred drug is streptomycin 7.5 to 10 mg/kg (up to 1 g) IM q 12 h for 7 to 14 days or, if in a bioterrorism setting, 15 mg/kg IM q 12 h. For children, the streptomycin dose is 10 to 15 mg/kg IM q 12 h. Chloramphenicol 12.5 to 25 mg/kg IV q 6 h is added if there is evidence of meningitis.

Alternatives to streptomycin include gentamicin 1 to 2 mg/kg IM or IV q 8 h, doxycycline 100 mg po q 12 h, chloramphenicol 12.5 to 25 mg/kg IV q 6 h (oral form not available in US), and ciprofloxacin 500 mg po q 12 h. However, relapses occasionally occur with these drugs, and they may not prevent node suppuration.

Continuous wet saline dressings are beneficial for primary skin lesions and may diminish the severity of lymphangitis and lymphadenitis. Surgical drainage of large abscesses is rarely necessary unless therapy is delayed. In ocular tularemia, applying warm saline compresses and using dark glasses give some relief. In severe cases, 2% homatropine 1 to 2 drops q 4 h may relieve symptoms. Intense headache usually responds to oral opioids (eg, oxycodone or hydrocodone with acetaminophen).

Prevention

When entering endemic areas, people should use tick-proof clothing and repellents. A thorough search for ticks should be done after leaving tick-infested areas. Ticks should be removed at once (see Sidebar 139-1 on p. 1283). When handling rabbits and rodents, especially in endemic areas, people should wear protective clothing, including rubber gloves and face masks, because organisms may be present in the animal and in tick feces on the animal's fur. Wild birds and game must be thoroughly cooked before eating. Water that may be contaminated must be disinfected before use.

No vaccine is currently available. Antibiotic prophylaxis with 14 days of oral doxycycline or ciprofloxacin is recommended after high-risk exposure (eg, a laboratory accident).

Chapter 136. Spirochetes

Introduction

The family Spirochaetales is distinguished by the helical shape of the bacteria. They are too thin to be visualized using routine microscopy but can be viewed using darkfield microscopy. There are 3 genera: *Treponema*, *Leptospira*, and *Borrelia*. The spirochetal disease syphilis is discussed on p. .

Bejel, Pinta, and Yaws

Bejel, pinta, and yaws (endemic treponematoses) are chronic, tropical, nonvenereal spirochetal infections spread by body contact. Symptoms of bejel are mucous-membrane and cutaneous lesions, followed by bone and skin gummas. Yaws causes periostitis and dermal lesions. Pinta lesions are confined to the dermis. Diagnosis is clinical and epidemiologic. Treatment is with penicillin.

The causative agents, *Treponema pallidum* subsp *endemicum* (bejel), *T. pallidum* subsp *pertenue* (yaws), and *T. carateum* (pinta), are morphologically and serologically indistinguishable from the agent of syphilis, *T. pallidum* subsp *pallidum*. As in syphilis, the typical course is an initial mucocutaneous lesion followed by diffuse secondary lesions, a latent period, and late destructive disease.

Transmission is by close skin contact—sexual or not—primarily between children living in conditions of poor hygiene. Bejel (endemic syphilis) occurs mainly in arid countries of the eastern Mediterranean and West Africa (Sahel). Transmission results from mouth-to-mouth contact or sharing eating and drinking utensils. Yaws (frambesia) occurs in humid equatorial countries where transmission is favored by scanty clothing and skin trauma. Pinta occurs among the natives of Mexico, Central America, and South America and is not very contagious. Transmission probably requires contact with broken skin.

Symptoms and Signs

Bejel begins in childhood as a mucous patch (usually on the buccal mucosa), which may go unnoticed; it is followed by papulosquamous and erosive papular lesions of the trunk and extremities that are similar to yaws. Periostitis of the leg bones is common. Later, gummatous lesions of the nose and soft palate develop.

Yaws, after an incubation period of several weeks, begins at the site of inoculation as a red papule that enlarges, erodes, and ulcerates. The surface resembles a strawberry, and the exudate is rich in spirochetes. The lesion heals but is followed after months to a year by successive generalized eruptions that resemble the primary lesion. These lesions often develop in moist areas of the axillae, skinfolds, and mucosal surfaces; they heal slowly and may recur. Keratotic lesions may develop on the palms and soles, causing painful ulcerations (crab yaws). Five to 10 yr later, destructive lesions may develop; they include periostitis (particularly of the tibia), proliferative exostoses of the nasal portion of the maxillary bone (goundou), juxta-articular nodules, gummatous skin lesions, and, ultimately, mutilating facial ulcers, particularly around the nose (gangosa).

Pinta lesions are confined to the dermis. They begin at the inoculation site as a small papule that enlarges and becomes hyperkeratotic; they develop mainly on the extremities, face, and neck. After 3 to 9 mo, further thickened and flat lesions (pintids) appear all over the body and over bony prominences. Still later, some lesions become slate blue or depigmented, resembling vitiligo.

Diagnosis

• Clinical evaluation

Diagnosis is based on the typical appearance of lesions in people from endemic areas. Serologic tests for syphilis (the Venereal Disease Research Laboratory [VDRL] and fluorescent treponemal antibody absorption tests) are positive; thus, differentiation from venereal syphilis is clinical. Early lesions are often

darkfield-positive for spirochetes and are indistinguishable from *T. pallidum* subsp *pallidum*.

Treatment

• Penicillin

Active disease is treated with 1 dose of penicillin benzathine 1.2 million units IM. Children < 45 kg should receive 600,000 units IM. Public health control includes active case finding and treatment of family and close contacts with penicillin benzathine.

Leptospirosis

Leptospirosis is an infection caused by one of several pathogenic serotypes of *Leptospira*. Symptoms are biphasic. Both phases involve acute febrile episodes; the 2nd phase sometimes includes hepatic, renal, and meningeal involvement. Diagnosis is by darkfield microscopy, culture, and serologic testing. Treatment is with doxycycline or penicillin.

Leptospirosis, a zoonosis occurring in many domestic and wild animals, may cause inapparent illness or serious, even fatal disease. There is a carrier state in which animals shed leptospires in their urine for years. Human infections are acquired by direct contact with infected urine or tissue or indirectly by contact with contaminated water or soil. Outbreaks frequently follow exposure to contaminated flood water. Abraded skin and exposed mucous membranes (conjunctival, nasal, oral) are the usual entry portals. Leptospirosis can be an occupational disease (eg, of farmers or sewer and abattoir workers), but in the US, most patients are exposed incidentally during recreational activities (eg, swimming in contaminated water). Dogs and rats are other common probable sources. The 40 to 100 annual US cases occur mainly in late summer and early fall. Because distinctive clinical features are lacking, probably many more cases are not diagnosed and reported.

Symptoms and Signs

The incubation period ranges from 2 to 20 (usually 7 to 13) days. The disease is characteristically biphasic. The septicemic phase starts abruptly, with headache, severe muscular aches, chills, fever, cough, chest pain, and, in some patients, hemoptysis. Conjunctival suffusion usually appears on the 3rd or 4th day. Splenomegaly and hepatomegaly are uncommon. This phase lasts 4 to 9 days, with recurrent chills and fever that often spikes to > 39° C. Defervescence follows. The 2nd, or immune, phase occurs between the 6th and 12th day of illness, correlating with appearance of antibodies in serum. Fever and earlier symptoms recur, and meningitis may develop. Iridocyclitis, optic neuritis, and peripheral neuropathy occur infrequently. If acquired during pregnancy, leptospirosis, even during the convalescent period, may cause abortion.

Weil's syndrome (icteric leptospirosis) is a severe form with jaundice and usually azotemia, anemia, diminished consciousness, and continued fever. Onset is similar to that of less severe forms. However, hemorrhagic manifestations, which are due to capillary injury and include epistaxis, petechiae, purpura, and ecchymoses, then develop and rarely progress to subarachnoid, adrenal, or GI hemorrhage. Thrombocytopenia may occur. Signs of hepatocellular and renal dysfunction appear from the 3rd to 6th day. Renal abnormalities include proteinuria, pyuria, hematuria, and azotemia. Hepatocellular damage is minimal, and healing is complete.

Mortality is nil in anicteric patients. With jaundice, the mortality rate is 5 to 10%; it is higher in patients > 60 yr.

Diagnosis

• Blood cultures

• Serologic testing

Similar symptoms can result from viral meningoencephalitis, hemolytic fever with renal syndrome due to

hantaviruses, other spirochetal infections, influenza, and hepatitis. The history of biphasic illness may help differentiate leptospirosis. Leptospirosis should be considered in any patient with FUO if they might have been exposed to leptospires.

Patients with suspected leptospirosis should have blood cultures, acute and convalescent (3- to 4-wk) antibody titers, CBC, serum chemistries, and liver function tests. Meningeal findings mandate lumbar puncture; the CSF cell count is between 10 and 1000/μL (usually < 500/μL), with predominantly mononuclear cells. CSF glucose is normal; protein is < 100 mg/dL. CSF bilirubin levels are higher than serum bilirubin levels.

The peripheral blood WBC count is normal or slightly elevated in most patients but may reach 50,000/μL in severely ill patients with jaundice. The presence of > 70% neutrophils helps differentiate leptospirosis from viral illnesses. Serum bilirubin is elevated out of proportion to elevations in serum amino-transferases. In jaundiced patients, bilirubin levels are usually < 20 mg/dL (< 342 μmol/L) but may reach 40 mg/dL (684 μmol/L) in severe infection.

Treatment

• Penicillin

• Doxycycline

Antibiotic therapy is most effective when begun early in the infection. In severe illness, penicillin G 5 to 6 million units IV q 6 h or ampicillin 500 to 1000 mg IV q 6 h is recommended. In less severe cases, doxycycline 100 mg po q 12 h, ampicillin 500 to 750 mg po q 6 h, or amoxicillin 500 mg po q 6 h may be given for 5 to 7 days. In severe cases, supportive care, including fluid and electrolyte therapy, is also important. Patient isolation is not required, but urine must be handled and disposed of carefully.

Doxycycline 200 mg po given once/wk during a period of known geographic exposure prevents disease.

Lyme Disease

Lyme disease is a tick-transmitted infection caused by *Borrelia burgdorferi*. Early symptoms include an erythema migrans rash, which may be followed weeks to months later by neurologic, cardiac, or joint abnormalities. Diagnosis is primarily clinical in early-stage disease, but serologic testing can help diagnose cardiac, neurologic, and rheumatologic complications that occur later in the disease. Treatment is with antibiotics such as doxycycline or ceftriaxone.

Epidemiology

Lyme disease was recognized in 1975 because of close clustering of cases in Lyme, Connecticut and is now the most commonly reported tick-borne illness in the US. It has been reported in 49 states, but > 90% of cases occur from Massachusetts to Maryland and in Wisconsin, Minnesota, California, and Oregon. Lyme disease also occurs in Europe, across the former Soviet Union, and in China and Japan. Onset is usually in the summer and early fall. Most patients are children and young adults living in heavily wooded areas.

Lyme disease is transmitted primarily by 4 *Ixodes* sp world wide: *Ixodes scapularis* (the deer tick) in the northeastern and north central US, *I. pacificus* in the western US, *I. ricinus* in Europe, and *I. persulcatus* in Asia. In the US, the white-footed mouse is the primary animal reservoir for *Borrelia burgdorferi* and the preferred host for nymphal and larval forms of the deer tick. Deer are hosts for adult ticks but do not carry *Borrelia*. Other mammals (eg, dogs) can be incidental hosts and can develop Lyme disease. In Europe, sheep host the organism.

Pathophysiology

B. burgdorferi enters the skin at the site of the tick bite. After 3 to 32 days, the organisms migrate locally in the skin around the bite, spread via the lymphatics to cause regional adenopathy or disseminate in

blood to organs or other skin sites. Initially, an inflammatory reaction (erythema migrans) occurs before significant antibody response to infection (serologic conversion).

Symptoms and Signs

Lyme disease has 3 stages:

• Early localized

• Early disseminated

• Late

The early and late stages are usually separated by an asymptomatic interval.

Early localized: Erythema migrans (EM), the hallmark and best clinical indicator of Lyme disease, is the first sign of the disease. It occurs in at least 75% of patients, beginning as a red macule or papule at the site of the tick bite, usually on the proximal portion of an extremity or the trunk (especially the thigh, buttock, or axilla), between 3 and 32 days after a tick bite (see Plate 60). The area expands, often with clearing between the center and periphery resembling a bull's eye, to a diameter ≤ 50 cm. Darkening erythema may develop in the center, which may be hot to the touch and indurated. Without therapy, EM typically fades within 3 to 4 wk.

Soon after onset, nearly one half of untreated patients develop multiple, usually smaller lesions without indurated centers. Cultures of biopsy samples of these secondary lesions have been positive, indicating dissemination of infection. EM generally lasts a few weeks (average, 3 to 4 wk). Evanescent lesions may appear during resolution. Mucosal lesions do not occur.

Early disseminated: Symptoms of early-disseminated disease begin days or weeks after the appearance of the primary lesion when the bacteria spread through the body. This musculoskeletal, flu-like syndrome, consisting of malaise, fatigue, chills, fever, headache, stiff neck, myalgias, and arthralgias, may last for weeks. Because symptoms are often nonspecific, the diagnosis is frequently missed if EM is absent; a high index of suspicion is required. Frank arthritis is rare at this stage. Less common are backache, nausea and vomiting, sore throat, lymphadenopathy, and splenomegaly.

Symptoms are characteristically intermittent and changing, but malaise and fatigue may linger for weeks. Some patients develop symptoms of fibromyalgia. Resolved skin lesions may reappear faintly, sometimes before recurrent attacks of arthritis, in late-stage disease.

Neurologic abnormalities develop in about 15% of patients within weeks to months of EM (generally before arthritis occurs), commonly last for months, and usually resolve completely. Most common are lymphocytic meningitis (CSF pleocytosis of about 100 cells/µL) or meningoencephalitis, cranial neuritis (especially Bell's palsy, which may be bilateral), and sensory or motor radiculoneuropathies, alone or in combination.

Myocardial abnormalities occur in about 8% of patients within weeks of EM. They include fluctuating degrees of atrioventricular block (1st-degree, Wenckebach, or 3rd-degree) and, rarely, myopericarditis with chest pain, reduced ejection fractions, and cardiomegaly.

Late: In untreated Lyme disease, the late stage begins months to years after initial infection. Arthritis develops in about 60% of patients within several months, occasionally up to 2 yr, of disease onset (as defined by EM). Intermittent swelling and pain in a few large joints, especially the knees, typically recur for several years. Affected knees commonly are much more swollen than painful; they are often hot, but rarely red. Baker cysts may form and rupture. Malaise, fatigue, and low-grade fever may precede or accompany arthritis attacks. In about 10% of patients, knee involvement is chronic (unremittent for ≥ 6 mo). Other late findings (occurring years after onset) include an antibiotic-sensitive skin lesion (acrodermatitis chronica atrophicans) and chronic CNS abnormalities, either polyneuropathy or a subtle encephalopathy with mood, memory, and sleep disorders.

Diagnosis

• Clinical evaluation, supported by acute and convalescent serologic testing

Cultures of blood and relevant body fluids (eg, CSF, joint fluid) may be obtained, primarily to diagnose other pathogens. Acute (IgM) and convalescent (IgG) antibody titers may be helpful; positive enzyme-linked immunosorbent assay (ELISA) titers should be confirmed by Western blot. However, sero-conversion may be late (eg, > 4 wk) or occasionally absent (eg, if patients received prior antibiotic therapy), and positive IgG titers alone represent previous exposure. PCR testing of CSF or synovial fluid is often positive when those sites are involved. Consequently, diagnosis depends on both test results and the presence of typical findings. A classic EM rash strongly suggests Lyme disease, particularly when supported by other elements (eg, recent tick bite, exposure to endemic area, typical systemic symptoms).

In the absence of rash, diagnosis is more difficult. Early-disseminated disease may mimic idiopathic RA in children and reactive arthritis and atypical RA in adults. Important negative RA findings in adults include usually absent morning stiffness, subcutaneous nodules, iridocyclitis, mucosal lesions, rheumatoid factor, and antinuclear antibodies.

In the US, human granulocytic anaplasmosis and babesiosis are also transmitted by *I. scapularis* and have a common geographic distribution in the northeastern and upper Midwest. Patients ill with any one of the diseases transmitted by *I. scapularis* may be concurrently infected with the other diseases it transmits. A clinician should suspect that patients with Lyme disease also have babesiosis if they have hemolytic anemia and thrombocytopenia or that they also have human granulocytic anaplasmosis if they have hepatitis, leukopenia, or thrombocytopenia. Human monocytotropic ehrlichiosis, which is caused by *Ehrlichia chaffeensis* and transmitted by the Lone Star tick, *Amblyomma americanum*, occurs mainly in the southeastern and south central US and is unlikely to be confused with Lyme disease.

Lyme disease may manifest with a musculoskeletal aseptic meningitis syndrome in summer. Although ehrlichiosis, a rickettsial infection, is transmitted by the same tick (see p.), clinical coinfection is rare. The lack of leukopenia, thrombocytopenia, elevated aminotransferases, and inclusion bodies in neutrophils helps distinguish Lyme disease from human granulocytic anaplasmosis. Lack of hemolytic anemia (unelevated LDH) and thrombocytopenia helps exclude babesiosis. Acute rheumatic fever is considered in the occasional patient with migratory polyarthralgias and either an increased PR interval or chorea (as a manifestation of meningoencephalitis). However, patients with Lyme disease rarely have heart murmurs or evidence of a preceding streptococcal infection.

Late-stage disease lacks axial involvement, which distinguishes it from spondyloarthropathies with peripheral joint involvement. Lyme disease may cause Bell's palsy and can mimic other causes of lymphocytic meningitis, or peripheral neuropathies.

In areas where Lyme disease is endemic, many patients report arthralgias, fatigue, difficulty concentrating, or other nonspecific symptoms. Without a history of EM or other symptoms of early-localized or early-disseminated Lyme disease, few of these patients actually have Lyme disease. In such patients, elevated IgG titers (with normal IgM titers) indicate past exposure, not current or persistent infection, and may lead to long and unnecessary courses of antibiotic therapy.

Treatment

• Multiple alternatives that vary with stage of disease but typically include amoxicillin, doxycycline, and ceftriaxone

Most features of Lyme disease respond to antibiotics, but treatment of early disease is most successful. In late-stage disease, antibiotics eradicate the bacteria, relieving the arthritis in most people. However, a few genetically predisposed people have persistent arthritis even after the infection has been eliminated because of continued inflammation.

Table 136-3 shows adult treatment regimens for various presentations of Lyme disease. Treatment in children is similar except that doxycycline is avoided in children < 8 yr and doses are adjusted based on

weight (see
Table 132-3 on p. 1185).

For symptomatic relief, NSAIDs may be used. Complete heart block may require a temporary pacemaker. Tense knee joints due to effusions require aspiration. Some genetically predisposed patients with arthritis of the knee that persists despite antibiotic therapy may respond to arthroscopic synovectomy.

Prevention

Precautions against tick bite (see Sidebar 139-1 on p. 1283) should be taken by people in endemic areas. Deer tick nymphs, which attack humans, are small and difficult to see. Once attached to the skin, they gorge on blood for days. Transmission of *B. burgdorferi* does not usually occur until the infected tick has been in place for > 36 h. Thus, searching for ticks after potential exposure and removing them promptly can help prevent infection.

A single dose of doxycycline 200 mg po has been shown to reduce the likelihood of Lyme disease after a deer tick bite. Patients with a known tick bite can easily be instructed to monitor the bite site and seek care if rash or other symptoms occur; the diagnostic dilemma of Lyme is most prominent when there is no history of tick bite.

[**Table 136-3.** Guidelines for Antibiotic Treatment of Lyme Disease in Adults*]

A vaccine, which had adverse effects similar to symptoms of Lyme disease and was only moderately effective, has been removed from the market.

Rat-Bite Fever

Rat-bite fever is caused by either *Streptobacillus moniliformis* or *Spirillum minus*. Symptoms of the streptobacillary form include fever, rash, and arthralgias. The spirillary form causes relapsing fever, rash, and regional lymphadenitis. Diagnosis is clinical and confirmed by culture and sometimes rising antibody titers. Treatment is with penicillin or doxycycline.

Rat-bite fever is transmitted to humans in up to 10% of rat bites. However, there may be no history of rat bite. Rat-bite fever is most commonly caused by rat bites but can be caused by the bite of any rodent or of a carnivore that preys on rodents. Both the streptobacillary and spirillary forms affect mainly urban dwellers living in crowded conditions and biomedical laboratory personnel. In the US and Europe, rat-bite fever is usually due to *S. moniliformis*; in Asia, it is usually due to *S. minus*.

Streptobacillary rat-bite fever: This form is caused by the pleomorphic gram-negative bacillus *S. moniliformis*, an organism present in the oropharynx of healthy rats. Epidemics have been associated with ingestion of unpasteurized milk contaminated by *S. moniliformis* (Haverhill fever), but infection is usually a consequence of a bite by a wild rat or mouse. Other rodents and weasels have also been implicated.

The primary wound usually heals promptly, but after an incubation period of 1 to 22 (usually < 10) days, a viral-like syndrome develops abruptly, causing chills, fever, vomiting, headache, and back and joint pains. Most patients develop a morbilliform, petechial, or vesicular rash on the hands and feet about 3 days later. Polyarthralgia or arthritis, usually affecting the large joints asymmetrically, develops in many patients within 1 wk and, if untreated, may persist for several days or months. Bacterial endocarditis and abscesses in the brain or other tissues are rare but serious. Some patients have infected pericardial effusion and infected amniotic fluid. Haverhill fever resembles percutaneously acquired rat-bite fever, but with more prominent pharyngitis and vomiting.

Diagnosis is confirmed by culturing the organism from blood or joint fluid. Measurable agglutinins develop during the 2nd or 3rd wk and are diagnostically important if the titer increases. PCR or enzyme-linked immunosorbent assay (ELISA) tests may be helpful. The WBC count ranges between 6,000 and 30,000/μL. The streptobacillary form usually can be differentiated clinically from the spirillary form.

Treatment involves amoxicillin 1 g po q 8 h, procaine penicillin G 600,000 units IM q 12 h, or penicillin V 500 mg po qid for 7 to 10 days. Erythromycin 500 mg po qid may be used for patients allergic to penicillin. Doxycycline 100 mg q 12 h for 14 days is an alternative.

Spirillary rat-bite fever (sodoku): *S. minus* infection is acquired through a rat bite or occasionally a mouse bite. The wound usually heals promptly, but inflammation recurs at the site after 4 to 28 (usually > 10) days, accompanied by a relapsing fever and regional lymphadenitis. A roseolar-urticarial rash sometimes develops but is less prominent than the streptobacillary rash. Systemic symptoms commonly accompany fever, but arthritis is rare. In untreated patients, 2- to 4-day cycles of fever usually recur for 4 to 8 wk, but febrile episodes rarely recur for > 1 yr.

Diagnosis is by direct visualization or culture of *Spirillum* from blood smears or tissue from lesions or lymph nodes, or by Giemsa stain or darkfield examination of blood from inoculated mice. The WBC count ranges between 5,000 and 30,000/μL. The Venereal Disease Research Laboratory (VDRL) results are false-positive in half the patients. The disease may easily be confused with malaria or *Borrelia recurrentis* infection; both are characterized by relapsing fever.

Treatment is the same as for the streptobacillary form.

Relapsing Fever

(Tick, Recurrent, or Famine Fever)

Relapsing fever is a recurring febrile disease caused by several species of *Borrelia* and transmitted by lice or ticks. Symptoms are recurrent febrile episodes with headache, myalgia, and vomiting lasting 3 to 5 days, separated by intervals of apparent recovery. Diagnosis is clinical, confirmed by staining of peripheral blood smears. Treatment is with a tetracycline or erythromycin.

The insect vector may be soft ticks of the genus *Ornithodoros* or the human body louse, depending on geographic location. Louseborne relapsing fevers are rare in the US and endemic only in the highlands of Central and East Africa and the Andes of South America; the tick-borne fevers are endemic in the Americas, Africa, Asia, and Europe. In the US, the disease is generally confined to the western states, where occurrence is highest between May and September.

The louse is infected by feeding on a febrile patient. If the louse is crushed on a new host, *Borrelia* are released and can enter abraded skin or bites. Intact lice do not transmit disease. Ticks acquire the spirochetes from rodent reservoirs. Humans are infected when spirochetes in the tick's saliva or excreta enter the skin rapidly as the tick bites. Congenital borreliosis has also been reported.

The mortality rate is generally < 5% with treatment but may be considerably higher in very young, pregnant, old, malnourished, or debilitated people or during epidemics of louse-borne fever.

Symptoms and Signs

Because the tick feeds transiently and painlessly at night, most patients do not report a history of tick bite but may report an overnight exposure to caves or rustic dwellings. When present, louse infestation is usually obvious.

The incubation period ranges from 3 to 11 days (median, 6 days). Sudden chills mark the onset, followed by high fever, tachycardia, severe headache, vomiting, muscle and joint pain, and often delirium. An erythematous macular or purpuric rash may appear early over the trunk and extremities. Conjunctival, subcutaneous, or submucous hemorrhages may be present. Fever remains high for 3 to 5 days, then clears abruptly, indicating a turning point in the disease. The duration of illness ranges from 1 to 54 days (median, 18 days). Later in the several weeks' course of the disease, jaundice, hepatomegaly, splenomegaly, myocarditis, and heart failure may occur, especially in louse-borne disease. Other symptoms may include ophthalmitis, iridocyclitis, exacerbation of asthma, and erythema multiforme. Meningismus is rare. Spontaneous abortion can occur.

The patient is usually asymptomatic for several days to ≥ 1 wk between the initial episode and the first relapse. Relapses, related to the cyclic development of the parasites, occur with a sudden return of fever and often arthralgia and all the former symptoms and signs. Jaundice is more common during relapse. The illness clears as before, but 2 to 10 similar episodes may follow at intervals of 1 to 2 wk. The episodes become progressively less severe, and patients eventually recover as they develop immunity.

Diagnosis

• Darkfield microscopy

The diagnosis is suggested by recurrent fever and confirmed by visualization of spirochetes in the blood during a febrile episode. The spirochetes may be seen on darkfield examination or Wright's- or Giemsa-stained thick and thin blood smears. (Acridine orange stain for examining blood or tissue is more sensitive than Wright's or Giemsa stain.) Serologic tests are unreliable. Mild polymorphonuclear leukocytosis may occur. Serologic tests for syphilis and Lyme disease may be falsely positive.

Differential diagnosis includes Lyme arthritis, malaria, dengue, yellow fever, leptospirosis, typhus, influenza, and enteric fevers.

Treatment

• Tetracycline, doxycycline, or erythromycin

In relapsing fever transmitted by ticks, tetracycline or erythromycin 500 mg po q 6 h is given for 5 to 10 days. A single 500-mg oral dose of either drug cures louse-transmitted fever. Doxycycline 100 mg po q 12 h for 5 to 10 days is also effective. Children < 8 yr are given erythromycin estolate 10 mg/kg po tid. When vomiting or severe disease precludes oral administration, doxycycline 1 to 2 mg/kg may be given IV q 12 to 24 h to children > 8 yr. Children < 8 yr are given penicillin G 25,000 units/kg IV q 6 h.

Therapy should be started early during fever. A Jarisch-Herxheimer reaction may occur within 2 h of starting therapy. Severity of the Jarisch-Herxheimer reaction may be lessened by giving acetaminophen 650 mg po 2 h before and 2 h after the first dose of doxycycline or erythromycin.

Dehydration and electrolyte imbalance should be corrected with parenteral fluids. Acetaminophen with oxycodone or hydrocodone may be used for severe headache. Nausea and vomiting should be treated with prochlorperazine 5 to 10 mg po or IM once/day to qid. If heart failure occurs, specific therapy is indicated.

Chapter 137. Neisseriaceae

Introduction

All pathogenic aerobic gram-negative cocci belong to the Neisseriaceae family, which is composed of 5 genera:

• *Acinetobacter*

• *Kingella*

• *Moraxella* (including 2 subgenera, *Moraxella* and *Branhamella*)

• *Neisseria*

• *Oligella*

Of these, *Neisseria* includes the most important human pathogens, *N. meningitidis* and *N. gonorrhoeae*. Numerous saprophytic Neisseriaceae commonly inhabit the oropharynx, vagina, or colon but rarely cause human disease. *Moraxella catarrhalis* causes otitis media in children and sinusitis. Over half a dozen other *Moraxella* sp and the related *Kingella kingae* cause infections in the CNS, respiratory tract, urinary tract, endocardium, bones, and joints.

Humans are the only reservoir of *Neisseria*, and person-to-person spread is the prime mode of transmission. Both *N. meningitidis* (meningococcus) and *N. gonorrhoeae* can exist in an asymptomatic carrier state. Carrier states are particularly important with meningococcus because of its association with epidemics. Gonorrhea is discussed on p. .

Acinetobacter Infections

Acinetobacter sp can cause suppurative infections in any organ system; these bacteria are often opportunists in hospitalized patients.

Acinetobacter is ubiquitous and can survive on dry surfaces for up to a month, increasing the likelihood of patients being colonized and medical equipment being contaminated. There are many species of *Acinetobacter*; all can cause human disease, but *A. baumannii* (AB) accounts for about 80% of infections.

Diseases Caused by Acinetobacter

AB infections typically occur in critically ill, hospitalized patients. Crude death rates associated with AB infection are 19 to 54%.

The most common site for infection is the respiratory system. *Acinetobacter* easily colonize tracheostomy sites and can cause community-acquired bronchiolitis and tracheobronchitis in healthy children and tracheobronchitis in immunocompromised adults. Hospital-acquired *Acinetobacter* pneumonias are frequently multilobar and complicated. Secondary bacteremia and septic shock are associated with a poor prognosis.

Acinetobacter sp can also cause suppurative infections (eg, abscesses) in any organ system, including the lungs, urinary tract, skin, and soft tissues; bacteremia may occur. Rarely, these organisms cause meningitis (primarily after neurosurgical procedures), cellulitis, or phlebitis in patients with an indwelling venous catheter, ocular infections, native or prosthetic valve endocarditis, osteomyelitis, septic arthritis, and pancreatic and liver abscesses.

The significance of isolates from clinical specimens is difficult to determine because they often represent colonization.

Risk factors: Risk factors for infection depend on the type of infection (hospital-acquired, community-acquired, multidrug resistant—see
Table 137-1).

Drug resistance: Recently, multidrug resistant (MDR) AB has emerged. Spread in ICUs has been attributed to colonized health care practitioners, contaminated common equipment, and contaminated parenteral nutrition solutions.

Treatment

• Typically empiric multidrug therapy for serious infections

In patients with localized cellulitis or phlebitis associated with a foreign body (eg, IV catheter, suture), removal of the foreign body plus local care is usually sufficient. Tracheobronchitis after endotracheal intubation may resolve with pulmonary toilet alone. Patients with more extensive infections should be treated with antibiotics and with debridement if necessary.

AB has long had intrinsic resistance to many antimicrobials. MDR-AB can be resistant to ≥ 3 classes of antimicrobials; some isolates are resistant to all. Possible options include a carbapenem (eg, meropenem, imipenem, doripenem), a β-lactam/β-lactamase inhibitor (eg, ampicillin/sulbactam), colistin, or a fluoroquinolone plus an aminoglycoside, rifampin, or both. Sulbactam (a β-lactamase inhibitor) has intrinsic bactericidal activity against many MDR-AB strains. Tigecycline, a glycylcycline antibiotic, is also effective; however, borderline activity and emergence of resistance during therapy has been reported.

Mild to moderate infections may respond to monotherapy. Traumatic wound infections

[**Table 137-1.** Risk Factors for *Acinetobacter* Infection]

can be treated with minocycline. Serious infections are treated with combination therapy—typically, imipenem, or a β-lactam/β-lactamase inhibitor plus an aminoglycoside.

To prevent spread, health care practitioners should use contact precautions (hand washing, barrier precautions) and appropriate ventilator care and cleaning for patients colonized or infected with MDR-AB.

Kingella Infections

Kingella organisms colonize the human respiratory tract. They cause skeletal infections, endocarditis, and bacteremia and, rarely, pneumonia, epiglottitis, meningitis, abscesses, and ocular infections.

Kingella are short, nonmotile, gram-negative coccobacilli that occur in pairs or short chains. The organisms are slow-growing and fastidious. *Kingella* are recovered from the human respiratory tract and are a rare cause of human disease.

Among *Kingella* species, *K. kingae* is the most frequent human pathogen; these organisms frequently colonize the respiratory mucous membranes. Children aged 6 mo to 4 yr have the highest rates of colonization and invasive disease from this and other respiratory tract pathogens such as *Moraxella catarrhalis* and *Streptococcus pneumoniae*. Infection has a seasonal distribution, with more cases in fall and winter.

Diseases Caused By *Kingella*

The most common manifestations of *K. kingae* disease are

• Skeletal infections

• Endocarditis

• Bacteremia

Rare manifestations include pneumonia, epiglottitis, meningitis, abscesses, and ocular infections.

The most common skeletal infection is septic arthritis, which most frequently affects large, weight-bearing joints, especially the knee and ankle. Osteomyelitis most frequently involves bones of the lower extremities. Onset is insidious, and diagnosis is often delayed. Hematogenous invasion of intervertebral disks can occur, most commonly in the lumbar intervertebral spaces.

Kingella endocarditis has been reported in all age groups. Endocarditis may involve native or prosthetic valves. *Kingella* is a component of the so-called HACEK group (*Haemophilus aphrophilus* and *H. parainfluenzae, Actinobacillus, Cardiobacterium, Eikenella, Kingella*—see p.), which includes fastidious gram-negative bacteria capable of causing endocarditis.

Diagnosis requires laboratory isolation from suspected fluids or tissues.

Treatment

• A penicillin or cephalosporin

Kingella organisms are generally susceptible to various penicillins and cephalosporins. However, antimicrobial susceptibility testing is needed to guide therapy. Other useful drugs include aminoglycosides, trimethoprim/sulfamethoxazole, tetracyclines, erythromycin, and ciprofloxacin.

Meningococcal Diseases

Meningococci (*Neisseria meningitidis*) cause meningitis and septicemia. Symptoms, usually severe, include headache, nausea, vomiting, photophobia, lethargy, rash, multiple organ failure, shock, and disseminated intravascular coagulation. Diagnosis is clinical, confirmed by culture. Treatment is penicillin or a 3rd-generation cephalosporin.

Worldwide, the incidence of endemic meningococcal disease is 0.5 to 5/100,000, with an increased number of cases during winter and spring in temperate climates. Local outbreaks occur most frequently in sub-Saharan Africa between Senegal and Ethiopia, an area known as the meningitis belt. In major African epidemics, attack rates range from 100 to 800/100,000.

In the US, the annual incidence ranges from 0.5 to 1.1/100,000. Most cases are sporadic, typically in children < 2 yr; < 2% occur in outbreaks. Outbreaks tend to occur in semiclosed communities (eg, military recruit camps, college dormitories, schools, day-care centers) and often involve patients aged 5 to 19 yr.

Diseases Caused by Meningococci

Over 90% of meningococcal infections involve

• Meningitis

• Septicemia

Infections of lungs, joints, respiratory passageways, GU organs, eyes, endocardium, and pericardium are less common.

Pathophysiology

Meningococci can colonize the oropharynx and nasopharynx of asymptomatic carriers. A combination of factors is probably responsible for transition from carrier state to invasive disease. Despite documented high rates of colonization, transition to invasive disease is rare and occurs primarily in previously uninfected patients. Transmission usually occurs via direct contact with respiratory secretions from a

nasopharyngeal carrier. Carrier rates rise dramatically during epidemics.

After invading the body, *N. meningitidis* causes meningitis and severe bacteremia in children and adults, resulting in profound vascular effects. Infection can rapidly become fulminant and is associated with a mortality rate of 10 to 15%. Of patients who recover, 10 to 15% have serious sequelae, such as permanent hearing loss, intellectual disability, or loss of phalanges or limbs.

Risk factors: Children aged 6 mo to 3 yr are the most frequently infected. Other high-risk groups include adolescents, military recruits, college freshmen living in dormitories, people with complement deficiencies, and microbiologists working with *N. meningitidis* isolates. Infection or vaccination confers serogroup-specific immunity.

Symptoms and Signs

Patients with meningitis frequently report fever, headache, and stiff neck (see also Acute Bacterial Meningitis on p.). Other symptoms include nausea, vomiting, photophobia, and lethargy. A maculopapular or hemorrhagic petechial rash often appears soon after disease onset. Meningeal signs are often apparent during physical examination. Fulminant meningococcemia syndromes include Waterhouse-Friderichsen syndrome (septicemia, profound shock, cutaneous purpura, adrenal hemorrhage), sepsis with multiple organ failure, shock, and disseminated intravascular coagulation. A rare, chronic meningococcemia causes recurrent mild symptoms.

Diagnosis

• Gram stain and culture

Neisseria are small, gram-negative cocci readily identified with Gram stain and by other standard bacteriologic identification methods. Serologic methods, such as latex agglutination and coagglutination tests, allow rapid presumptive diagnosis of *N. meningitides* in blood, CSF, synovial fluid, and urine. However, both positive and negative results should be confirmed by culture. PCR for *N. meningitidis* has been developed but is not commercially available.

Treatment

• Ceftriaxone

• Dexamethasone

While awaiting definitive identification of the causal organism, immunocompetent adults suspected of having meningococcal infection are given a 3rd-generation cephalosporin (eg, cefotaxime 2 g IV q 6 h, ceftriaxone 2 g IV q 12 h) plus vancomycin 500 to 750 mg IV q 6 h or 1 g IV q 12 h or q 8 h. In immunocompromised patients and patients > 50 yr, coverage for *Listeria monocytogenes* should be considered by adding ampicillin 2 g IV q 4 h.

Once *N. meningitidis* has been definitively identified, the preferred treatment is ceftriaxone 2 g IV q 12 h or penicillin 4 million units IV q 4 h.

Corticosteroids decrease the incidence of neurologic complications in children and adults. When corticosteroids are used, they should be given with or before the first dose of antibiotics. Dexamethasone 0.15 mg/kg IV q 6 h in children (10 mg q 6 h in adults) is given for 4 days.

Prevention

Antibiotic prophylaxis: Close contacts of people with meningococcal disease are at increased risk of acquiring disease and should receive a prophylactic antibiotic. Options include

• Rifampin 600 mg (for children > 1 mo, 10 mg/kg; for children < 1 mo, 5 mg/kg) po q 12 h for 4 doses

• Ceftriaxone 250 mg (for children < 15 yr, 125 mg) IM for 1 dose

• In adults, a fluoroquinolone (ciprofloxacin or levofloxacin 500 mg or ofloxacin 400 mg) po for 1 dose

Azithromycin is not routinely recommended, but a recent study showed that a single 500-mg dose was equivalent to rifampin for chemoprophylaxis and so could be an alternative for patients with contraindications to recommended drugs.

Ciprofloxacin-resistant meningococcal disease has been reported in several countries (Greece, England, Wales, Australia, Spain, Argentina, France, India). More recently, 2 US states (North Dakota, Minnesota) reported ciprofloxacin-resistant meningococci and so recommended that ciprofloxacin chemoprophylaxis not be used as preventive treatment for people who have had close contact with someone diagnosed with meningococcal disease.

Vaccination: A meningococcal conjugate vaccine is available in the US. The vaccine includes 4 of the 5 serogroups of meningococcus (all but B). A one-time routine vaccination is recommended for all children between the age of 11 and 18 yr. Vaccination is also recommended for people who are aged 19 to 55 and at risk, including military recruits, college freshmen living in a dormitory, travelers to hyperendemic or epidemic areas, and people with laboratory or industrial exposure to *N. meningitidis* aerosols. Adults and children aged 2 to 10 yr with terminal complement component deficiencies or functional or actual asplenia should also be vaccinated.

Moraxella Catarrhalis Infection

***Moraxella catarrhalis* causes ear and upper and lower respiratory infections.**

Previously classified as *Micrococcus*, then *Neisseria*, and also known as *Branhamella catarrhalis*, this organism is a frequent cause of otitis media in children, acute and chronic sinusitis at all ages, and lower respiratory infection in adults with chronic lung disease. It is the 2nd most common bacterial cause of COPD exacerbations after nontypeable *Haemophilus influenzae. M. catarrhalis* pneumonia resembles pneumococcal pneumonia. Although bacteremia is rare, half of patients die within 3 mo because of intercurrent diseases.

The prevalence of *M. catarrhalis* colonization depends on age. About 1 to 5% of healthy adults have upper respiratory tract colonization. Nasopharyngeal colonization with *M. catarrhalis* is common throughout infancy, may be increased during winter months, and is a risk factor for acute otitis media; early colonization is a risk factor for recurrent otitis media. Substantial regional differences in colonization rates occur. Living conditions, hygiene, environmental factors (eg, household smoking), genetic characteristics of the populations, host factors, and other factors may contribute to these differences.

The organism appears to spread contiguously from its colonizing position in the respiratory tract to the infection site.

There is no pathognomonic feature of *M. catarrhalis* otitis media, acute or chronic sinusitis, or pneumonia. In lower respiratory disease, patients experience increased cough, purulent sputum production, and increased dyspnea.

These gram-negative cocci resemble *Neisseria* sp but can be readily distinguished by routine biochemical tests after culture isolation from infected fluids or tissues.

All strains now produce β-lactamase. The organism is generally susceptible to β-lactam/β-lactamase inhibitors, sulfamethoxazole, tetracyclines, extended-spectrum oral cephalosporins, aminoglycosides, macrolides, and fluoroquinolones.

Oligella Infections

***Oligella* sp causes infection primarily of the GU tract.**

The genus *Oligella* contains 2 species, *Oligella urethralis* and *O. ureolytica.*

O. urethralis is a commensal of the GU tract, and most clinical isolates are from the urine, predominantly from men. Although symptomatic infections are rare, bacteremia, septic arthritis that mimics gonococcal arthritis, and peritonitis have been reported.

O. ureolytica also occurs primarily in the urine, usually from patients with long-term urinary catheters or other urinary drainage systems. These patients have a propensity to develop urinary stones, possibly because the organism hydrolyzes urea and alkalinizes urine, leading to precipitation of phosphates. Bacteremia has occurred in a patient with obstructive uropathy.

Diagnosis is by culture.

Because these organisms are rarely isolated, antimicrobial susceptibility data are limited; most are sensitive to β-lactam antibiotics. However, a β-lactam-producing strain and strains resistant to ciprofloxacin have been identified.

Chapter 138. Chlamydia and Mycoplasmas

Chlamydia

Three species of *Chlamydia* cause human disease, including sexually transmitted diseases and pneumonias. Most are susceptible to azithromycin, doxycycline, and some fluoroquinolones.

Chlamydiae are nonmotile, obligate intracellular organisms. Although originally considered viruses because they require a cellular host, they are now known to be bacteria; they contain DNA, RNA, and ribosomes and make their own proteins and nucleic acids. However, because they synthesize most of their own metabolic intermediates, they cannot make their own ATP and thus are energy parasites.

Three species cause human disease:

• *Chlamydia trachomatis*

• *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*

• *Chlamydophila* (formerly *Chlamydia*) *psittaci*

C. trachomatis has 18 immunologically defined serovars. Serovars A, B, Ba, and C cause trachoma and inclusion conjunctivitis; D through K cause sexually transmitted diseases (STDs) localized to mucosal surfaces; L1, L2, and L3 cause STDs that lead to invasive lymph node disease (lymphogranuloma venereum). In the US, *C. trachomatis* is the most common bacterial cause of STDs, including nongonococcal urethritis (see p.) and epididymitis in men; cervicitis, urethritis, and pelvic inflammatory disease in women; and proctitis, lymphogranuloma venereum, and reactive arthritis (Reiter's syndrome) in both sexes. Maternal transmission of *C. trachomatis* causes neonatal conjunctivitis and pneumonia. The organism is occasionally isolated from the throat in adults but rarely causes symptomatic pharyngitis.

C. pneumoniae can cause pneumonia (especially in children and young adults) that may be clinically indistinguishable from pneumonia caused by *Mycoplasma pneumoniae*. In some patients with *C. pneumoniae*, pneumonia, hoarseness, and sore throat may precede coughing, which may be persistent and complicated by bronchospasm. From 6 to 19% of community-acquired pneumonia cases are due to *C. pneumoniae*, but chlamydial pneumonia is uncommon among children < 5 yr. No seasonal variations in occurrence have been observed. The organism has been found in atheromatous lesions, and infection may be associated with increased risk of coronary artery disease, although proof of a connection has not yet been established.

C. psittaci causes psittacosis. Strains causing human disease are usually transmitted from psittacine birds (eg, parrots), causing a disseminated disease characterized by pneumonitis.

Diagnosis

• Clinical evaluation

• Sometimes nucleic acid-based testing

The diagnosis is sometimes made without testing (eg, in men with typical nongonococcal urethritis). However, because many cases are asymptomatic, especially in women, routine testing for genital infection has been recommended and is increasingly common. In cases of urethritis, diagnosis is often made by excluding gonorrhea as a cause or by presuming that both chlamydial infection and gonorrhea are present.

C. trachomatis can be isolated by diagnostic cell culture but is best identified in genital samples using nucleic acid amplification tests (NAATs) such as PCR because these tests are more sensitive than cell culture and have less stringent sample handling requirements. NAATs for genital infection can be done

using noninvasively obtained samples, such as urine or vaginal swabs obtained by the patient or clinician. An enzyme-linked immunosorbent assay (ELISA) or a direct immunofluorescent slide test can detect antigens in genital and ocular infections, but both are less sensitive than culture or NAATs. Serologic tests are useful in diagnosing pneumonia in infants and lymphogranuloma venereum.

A primary clue to diagnosis of *C. psittaci* infection is close contact with birds, typically parrots or parakeets.

Screening: Because chlamydial genital infection is so common and often causes mild or nonspecific symptoms (particularly in women), routine screening of asymptomatic people at high risk of STDs is recommended. People who should be screened include

• People with a history of a previous STD

• People with high-risk behaviors

• Sexually active adolescents and young adults < 24 yr

• Pregnant women < 24 yr

Treatment

• Azithromycin or doxycycline

Uncomplicated lower genital tract infection is typically treated with a single dose of azithromycin (1 g po) or with a 7-day regimen of doxycycline (100 mg po bid) or some fluoroquinolones (eg, levofloxacin 500 mg po once/day). Treatment of presumed chlamydial infection is routine when gonorrhea is present (see also p. 1473). Pelvic inflammatory disease, lymphogranuloma venereum, or epididymitis is usually treated for 2 wk.

Specific infections are discussed elsewhere in THE MANUAL: Psittacosis and *C. pneumoniae* pneumonia on p. 1924, lymphogranuloma venereum and urethritis on p. 1474, epididymitis on p. 2455, reactive arthritis on p. 343, neonatal conjunctivitis and neonatal pneumonia on pp. 2824 and 2832, and trachoma and inclusion conjunctivitis on p. 583.

Mycoplasmas

Mycoplasmas are ubiquitous bacteria that differ from other prokaryotes in that they lack a cell wall. *Mycoplasma pneumoniae* is a common cause of pneumonia, particularly community-acquired. Increasing evidence suggests that *M. genitalium* and *Ureaplasma urealyticum* cause some cases of nongonococcal urethritis. They (and *M. hominis*) are often present in patients with other urogenital infections (eg, vaginitis, cervicitis, pyelonephritis, pelvic inflammatory disease) and some nonurogenital infections, but whether they cause these infections is not clear.

Mycoplasmas are not visible with light microscopy. Culture is technically difficult and often unavailable, but laboratory diagnosis is sometimes possible with DNA probes or by detection of antibodies or antigens; frequently, diagnosis must be clinical.

Macrolides are usually the antimicrobials of choice. Most species are also sensitive to fluoroquinolones and tetracyclines.

Chapter 139. Rickettsiae and Related Organisms

Introduction

Rickettsial diseases (rickettsioses) and related diseases (ehrlichiosis, Q fever) are caused by a group of gram-negative, obligately intracellular coccobacilli. Most have an arthropod vector. Symptoms usually include sudden-onset fever with severe headache, malaise, prostration, and, in most cases, a characteristic rash. Diagnosis is clinical, confirmed by immunofluorescence assay or PCR. Treatment is with tetracyclines or chloramphenicol.

Although rickettsiae require living cells for growth, they are true bacteria because they have metabolic enzymes and cell walls, use O$_2$, and are susceptible to antibiotics. Rickettsiae (except *Coxiella burnetii*, the causative agent of Q fever, which is no longer classified with the Rickettsiae) have an animal reservoir and usually an arthropod vector that infects humans (see Table 139-1).

Rickettsiae multiply at the site of arthropod attachment and often produce a local lesion (eschar). They penetrate the skin or mucous membranes; some (*Rickettsia rickettsii*) multiply in the endothelial cells of small blood vessels, causing vasculitis, and others (*Ehrlichia* sp) replicate in WBCs. The endovasculitis of *R. rickettsii* causes a rash, encephalitic signs, and gangrene of skin and tissues. Patients seriously ill with a rickettsial disease of the typhus or spotted fever group or with ehrlichiosis may have ecchymotic skin necrosis, digital gangrene, circulatory collapse, shock, oliguria, anuria, azotemia, anemia, hyponatremia, hypochloremia, edema, delirium, and coma.

Diagnosis

• Clinical features

• Biopsy of rash

• Serologic testing not useful acutely

• PCR for *Ehrlichia* sp

Differentiating rickettsial from other infections:

Rickettsial and related diseases must be differentiated from other acute infections, primarily meningococcemia, rubeola, and rubella. A history of louse or flea contact, tick bite, or presence in a known endemic area is helpful, but such history is often absent. Clinical features may help distinguish diseases:

• Meningococcemia: The rash may be pink, macular, maculopapular, or petechial in the subacute form and petechially confluent or ecchymotic in the fulminant form. The rash develops rapidly in acute meningococcal disease and, when ecchymotic, is usually tender when palpated.

• Rubeola: The rash begins on the face, spreads to the trunk and arms, and soon becomes confluent.

• Rubella: The rash usually remains discrete. Postauricular lymph node enlargement and lack of toxicity suggest rubella.

Differentiating among rickettsial diseases: Rickettsial and related diseases must also be differentiated from each other. Clinical features allow some differentiation, but overlap is considerable:

• Rocky Mountain spotted fever (RMSF): The rash usually appears on about the 4th febrile day as blanching macules on the extremities and gradually becomes petechial as it spreads to the trunk, palms, and soles over several days. Some patients with RMSF never develop a rash.

• Epidemic typhus: The rash usually appears initially in the axillary folds and on the trunk. Later, it spreads peripherally, rarely involving the palms, soles, and face. Severe physiologic and pathologic abnormalities similar to those of RMSF occur.

• Murine typhus: The rash is nonpurpuric, nonconfluent, and less extensive, and renal and vascular complications are uncommon.

• Scrub typhus: Manifestations are similar to those of RMSF and epidemic typhus.

[**Table 139-1.** Diseases Caused by *Rickettsia, Ehrlichia*, and *Coxiella* Spp]

However, scrub typhus occurs in different geographic areas, and frequently, an eschar develops with satellite adenopathy.

• Rickettsialpox: This disease is mild, and the rash, in the form of vesicles with surrounding erythema, is sparse and may resemble varicella.

• African tick bite fever (due to *R. Africae*): Symptoms are similar to those of other rick-ettsial diseases. The rash is characterized by multiple black eschars on the distal extremities with regional adenopathy.

Testing: Knowledge of residence and recent travel often helps in diagnosis because many rickettsiae are localized to certain geographic areas. However, testing is usually required.

The most useful tests for *R. rickettsii* are indirect immunofluorescence assay (IFA) and PCR of a biopsy specimen of the rash. Culture is difficult and not clinically useful. For *Ehrlichia* sp, PCR of blood is the best test. Serologic tests are not useful for acute diagnosis because they usually become positive only during convalescence.

Treatment

• Tetracyclines

Because diagnostic tests can take time and may be insensitive, antibiotics are usually begun presumptively to prevent significant deterioration, death, and prolonged recovery. Tetracyclines are first-line treatment: doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. IV preparations are used in patients too ill to take oral drugs. Although tetracyclines can cause tooth staining in children, experts think that a course of doxycycline is warranted. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment. Both drugs are rickettsiostatic, not rickettsicidal. Ciprofloxacin and other fluoroquinolones are effective against certain rickettsiae, but extensive clinical experience is lacking.

Because severely ill patients with RMSF or epidemic typhus may have a marked increase in capillary permeability in later stages, IV fluids should be given cautiously to maintain BP while avoiding worsening pulmonary and cerebral edema. Heparin is not recommended in patients who develop disseminated intravascular coagulation.

Eastern Tick-Borne Rickettsioses

Eastern tick-borne rickettsioses (ETBR) are caused by various rickettsiae transmitted by ixodid ticks. Symptoms are an initial skin lesion, satellite adenopathy, and an erythematous maculopapular rash.

ETBR include North Asian tick-borne rickettsiosis, Queensland tick typhus, African tick typhus, and Mediterranean spotted fever (boutonneuse fever). The causative agents belong to the spotted fever group of rickettsiae.

The epidemiology of these tick-borne rick-ettsioses resembles that of spotted fever in the Western Hemisphere. Ixodid ticks and wild animals maintain the rickettsiae in nature. If humans intrude

accidentally into the cycle, they become infected. In certain areas, the cycle of boutonneuse fever involves domiciliary environments, with the brown dog tick, *Rhipicephalus sanguineus*, as the dominant vector.

Symptoms and Signs

The symptoms and signs are similar for all ETBR and generally milder than with spotted fever. After an incubation period of 5 to 7 days, fever, malaise, headache, and conjunctival injection develop. With the onset of fever, a small buttonlike ulcer 2 to 5 mm in diameter with a black center appears (an eschar or, in boutonneuse fever, tache noire). Usually, the regional or satellite lymph nodes are enlarged. On about the 4th day of fever, a red maculopapular rash appears on the forearms and extends to most of the body, including the palms and soles. Fever lasts into the 2nd wk.

Complications and death are rare except among elderly or debilitated patients. However, the disease should not be ignored; a fulminant form of vasculitis can occur.

Diagnosis

For diagnosis, see p. .

Treatment

• Doxycycline or ciprofloxacin

Treatment is doxycycline 100 mg po bid for 5 days or ciprofloxacin 500 to 750 mg po bid for 5 days. Measures can be taken to prevent tick bites (see Sidebar 139-1).

Epidemic Typhus

(European, Classic, or Louse-Borne Typhus; Jail Fever)

Epidemic typhus is caused by *Rickettsia prowazekii*. Symptoms are prolonged high fever, intractable headache, and a maculopapular rash.

Humans are the natural reservoir for *R. prowazekii*, which is prevalent worldwide and transmitted by body lice when louse feces are scratched or rubbed into bite or other wounds (or sometimes the mucous membranes of the eyes or mouth). In the US, humans may occasionally contract epidemic typhus after contact with flying squirrels.

Fatalities are rare in children < 10 yr, but mortality increases with aging and may reach 60% in untreated patients > 50 yr.

Symptoms and Signs

After an incubation period of 7 to 14 days, fever, headache, and prostration suddenly occur. Temperature reaches 40° C in several days and remains high, with slight morning remission, for about 2 wk. Headache is generalized and intense. Small, pink macules, which appear on the 4th to 6th day, rapidly cover the body, usually in the axillae and on the upper trunk and not on the palms, soles, and face. Later, the rash becomes dark and maculopapular. In severe cases, the rash becomes petechial and hemorrhagic. Splenomegaly sometimes occurs. Hypotension occurs in most seriously ill patients. Vascular collapse, renal insufficiency, encephalitic signs, ecchymosis with gangrene, and pneumonia are poor prognostic signs.


Sidebar 139-1 Tick Bite Prevention

Preventing tick access to skin includes

• Staying on paths and trails

• Tucking trousers into boots or socks

• Wearing long-sleeved shirts

• Applying repellents with diethyltoluamide (DEET) to skin surfaces

DEET should be used cautiously in very young children because toxic reactions have been reported. Permethrin on clothing effectively kills ticks. Frequent searches for ticks, particularly in hairy areas and on children, are essential in endemic areas.

Engorged ticks should be removed with care and not crushed between the fingers because crushing the tick may result in disease transmission. The tick's body should not be grasped or squeezed. Gradual traction on the head with a small forceps dislodges the tick. The point of attachment should be swabbed with alcohol. Petroleum jelly, alcohol, lit matches, and other irritants are not effective and should not be used.

No practical means are available to rid entire areas of ticks, but tick populations may be reduced in endemic areas by controlling small-animal populations.

Actual size

| Deer tick (nymph) | Deer tick (adult) | Dog tick (adult) |
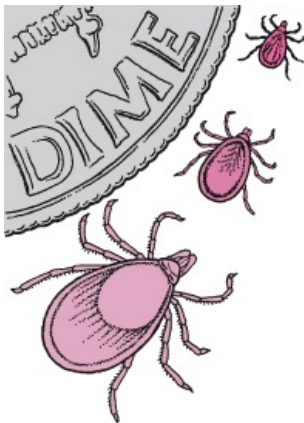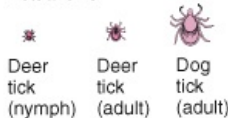
Diagnosis

Louse infestation is usually obvious and strongly suggests typhus if history (eg, living in or visiting an endemic area) suggests possible exposure. For details of diagnosis, see p. .

Treatment

• Doxycycline

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment.

Prevention

Immunization and louse control are highly effective for prevention. However, vaccines are not available in the US. Lice may be eliminated by dusting infested people with malathion or lindane.

Brill-Zinsser Disease

Brill-Zinsser disease is a recrudescence of epidemic typhus, occurring years after an initial attack.

Patients with Brill-Zinsser disease acquired epidemic typhus earlier or lived in an endemic area. Apparently, when host defenses falter, viable organisms retained in the body are activated, causing recurrent typhus; thus, disease is sporadic, occurring at any season and in the absence of infected lice. Lice that feed on patients may acquire and transmit the agent.

Symptoms and signs are almost always mild and resemble those of epidemic typhus, with similar circulatory disturbances and hepatic, renal, and CNS changes. The remittent febrile course lasts about 7 to 10 days. The rash is often evanescent or absent. Mortality is nil.

For diagnosis and treatment, see p. .

Murine (Endemic) Typhus

(Rat-Flea Typhus; Urban Typhus of Malaya)

Murine typhus is caused by *Rickettsia typhi*, which is transmitted to humans by rat fleas; it is clinically similar to but milder than epidemic typhus, causing chills, headache, fever, and rash.

Animal reservoirs include wild rats, mice, and other rodents. Rat fleas and probably cat fleas transmit the agent to humans. Distribution is sporadic but worldwide; the incidence is low but higher in rat-infested areas.

After an incubation of 6 to 18 days (mean 10 days), a shaking chill accompanies headache and fever. The fever lasts about 12 days; then temperature gradually returns to normal. The rash and other manifestations are similar to those of epidemic typhus but are much less severe. The early rash is sparse and discrete. Mortality is low but is higher in elderly patients.

Diagnosis

Murine typhus is identified by immunofluorescence assay (IFA), immunohistology of a skin biopsy, PCR, and enzyme-linked immunosorbent assay (ELISA).

Treatment

• Doxycycline

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment. (For details of treatment, see p. .)

Incidence has been decreased by reducing rat and rat flea populations. No effective vaccine exists.

Rickettsialpox

(Vesicular Rickettsiosis)

Rickettsialpox is caused by *Rickettsia akari*. Symptoms are an initial local lesion and a generalized papulovesicular rash.

Rickettsialpox occurs in many areas of the US and in Russia, Korea, and Africa. The vector, a small, colorless mite, is widely distributed. It infects the house mouse and some species of wild mice. Humans may be infected by chigger (mite larvae) or adult mite bites.

An eschar appears about 1 wk before onset of fever as a small papule 1 to 1.5 cm in diameter, then develops into a small ulcer with a dark crust that leaves a scar when it heals. Regional lymphadenopathy is present. An intermittent fever lasts about 1 wk, with chills, profuse sweating, headache, photophobia, and muscle pains. Early in the febrile course, a generalized maculopapular rash with intraepidermal vesicles appears, sparing the palms and soles. The disease is mild; no deaths have been reported.

For details of diagnosis, see p. .

Treatment is doxycycline 100 mg po bid for 5 days or ciprofloxacin 750 mg po bid for 5 days.

For prophylaxis, mouse harborages must be destroyed, and the vector controlled by residual insecticides.

Rocky Mountain Spotted Fever

(Spotted Fever; Tick Fever; Tick Typhus)

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and transmitted by ixodid ticks. Symptoms are high fever, severe headache, and rash.

Epidemiology

RMSF is limited to the Western Hemisphere. Initially recognized in the Rocky Mountain states, it occurs in practically all of the US, especially the Atlantic states, and throughout Central and South America. In humans, infection occurs mainly from March to September, when adult ticks are active and people are most likely to be in tick-infested areas. In southern states, sporadic cases occur throughout the year. The incidence is highest in children < 15 yr and in people who frequent tick-infested areas for work or recreation.

Hard-shelled ticks (family Ixodidae) harbor *R. rickettsii*, and infected females transmit the agent to their progeny. These ticks are the natural reservoirs. *Dermacentor andersoni* (wood tick) is the principal vector in the western US. *D. variabilis* (dog tick) is the vector in the eastern and southern US. RMSF is probably not transmitted directly from person to person.

Pathophysiology

Small blood vessels are the sites of the characteristic pathologic lesions. Rickettsiae propagate within damaged endothelial cells, and vessels may become blocked by thrombi, producing vasculitis in the skin, subcutaneous tissues, CNS, lungs, heart, kidneys, liver, and spleen. Disseminated intravascular coagulation often occurs in severely ill patients (see p. 976).

Symptoms and Signs

The incubation period averages 7 days but varies from 3 to 12 days; the shorter the incubation period, the more severe the infection. Onset is abrupt, with severe headache, chills, prostration, and muscular pains. Fever reaches 39.5 to 40° C within several days and remains high (for 15 to 20 days in severe cases), although morning remissions may occur. Between the 1st and 6th day of fever, most patients develop a rash on the wrists, ankles, palms, soles, and forearms that rapidly extends to the neck, face, axillae, buttocks, and trunk. Initially macular and pink, it becomes maculopapular and darker. In about 4 days, the lesions become petechial and may coalesce to form large hemorrhagic areas that later ulcerate.

Neurologic symptoms include headache, restlessness, insomnia, delirium, and coma, all indicative of encephalitis. Hypotension develops in severe cases. Hepatomegaly may be present, but jaundice is infrequent. Nausea and vomiting are common. Localized pneumonitis may occur. Untreated patients may develop pneumonia, tissue necrosis, and circulatory failure, sometimes with brain and heart damage. Cardiac arrest with sudden death occasionally occurs in fulminant cases.

Diagnosis

• Specifics of diagnosis on p. 1280.

Clinicians should suspect RMSF in any seriously ill patient who lives in or near a wooded area anywhere in the Western Hemisphere and has unexplained fever, headache, and prostration, with or without a history of tick contact. A history of tick bite is elicited in about 70% of patients.

Treatment

• Doxycycline

Starting antibiotics early significantly reduces mortality, from about 20 to 5%, and prevents most complications. If patients who have been in an endemic area have a tick bite but no clinical signs, antibiotics should not be given immediately.

If fever, headache, and malaise occur with or without a rash, antibiotics should be started promptly. Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment.

No effective vaccine is available. Measures can be taken to prevent tick bites (see Sidebar 139-1).

Scrub Typhus

(Tsutsugamushi Disease; Mite-Borne Typhus; Tropical Typhus)

Scrub typhus is a mite-borne disease caused by *Rickettsia tsutsugamushi*. Symptoms are fever, a primary lesion, a macular rash, and lymphadenopathy.

R. tsutsugamushi is transmitted by trombiculid mites, which feed on forest and rural rodents, including rats, voles, and field mice. Human infection follows a chigger (mite larva) bite.

Symptoms

After an incubation period of 6 to 21 days (mean 10 to 12 days), fever, chills, headache, and generalized lymphadenopathy start suddenly. At onset of fever, an eschar often develops at the site of the chigger bite. The typical lesion, common in whites but rare in Asians, begins as a red, indurated lesion about 1 cm in diameter; it eventually vesiculates, ruptures, and becomes covered with a black scab. Regional lymph nodes enlarge. Fever rises during the 1st wk, often to 40 to 40.5° C. Headache is severe and common, as is conjunctival injection. A macular rash develops on the trunk during the 5th to 8th day of fever, often extending to the arms and legs. It may disappear rapidly or become maculopapular and intensely colored. Cough is present during the 1st wk of fever, and pneumonitis may develop during the 2nd wk.

In severe cases, pulse rate increases; BP drops; and delirium, stupor, and muscular twitching develop. Splenomegaly may be present, and interstitial myocarditis is more common than in other rickettsial diseases. In untreated patients, high fever may persist ≥ 2 wk, then falls gradually over several days. With therapy, defervescence usually begins within 36 h. Recovery is prompt and uneventful.

Diagnosis

For details of diagnosis, see p. 1280.

Treatment

• Doxycycline

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po

or IV qid for 7 days is 2nd-line treatment.

Clearing brush and spraying infested areas with residual insecticides eliminate or decrease mite populations. Insect repellents (eg, diethyltoluamide [DEET]) should be used when exposure is likely.

Ehrlichiosis

Ehrlichiosis is caused by rickettsial-like bacteria of the genus *Ehrlichia* transmitted to humans by ticks. Symptoms resemble those of Rocky Mountain spotted fever except that a rash is much less common. Onset of illness, with fever, chills, headache, and malaise, is abrupt.

Most cases have been identified in the southeastern and south central US. Three species of *Ehrlichia* are human pathogens in the US: *E. chaffeensis* causes human monocytic ehrlichiosis; *Anaplasma phagocytophila* (formerly *E. phagocytophila*) and *E. ewingii* cause human granulocytic ehrlichiosis. The difference in the primary target cell results in only minor differences in clinical manifestations.

These obligate, intracellular bacteria appear as small cytoplasmic inclusions in lymphocytes and neutrophils. Infections are transmitted to humans via tick bites, sometimes via contact with animals that carry the brown dog tick or deer tick.

Symptoms and Signs

Although some infections are asymptomatic, most cause an abrupt onset of illness with fever, chills, headache, and malaise, usually beginning about 12 days after the tick bite. Some patients develop a maculopapular or petechial rash involving the trunk and extremities, although rash is rare with *E. ewingii*. Abdominal pain, vomiting and diarrhea, disseminated intravascular coagulation, seizures, and coma may occur.

Diagnosis

• PCR testing of a blood sample

Diagnostic serologic tests are available, but PCR of blood is more sensitive and specific and can result in an early diagnosis. Cytoplasmic ehrlichial inclusions in monocytes or neutrophils may be detected. Blood and liver functions tests may detect hematologic and hepatic abnormalities, such as leukopenia, thrombocytopenia, and elevated aminotransferase levels.

Treatment

• Doxycycline

Treatment is best started before laboratory results return. When treatment is started early, patients generally respond rapidly and well. A delay in treatment may lead to serious complications, including viral and fungal super-infections and death in 2 to 5%.

Primary treatment is doxycycline 200 mg po once followed by 100 mg bid until the patient improves, has been afebrile for 24 to 48 h, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment.

Measures can be taken to prevent tick bites (see Sidebar 139-1).

Q Fever

Q fever is an acute or chronic disease caused by the rickettsial-like bacillus *Coxiella burnetii*. Acute disease causes sudden onset of fever, headache, malaise, and interstitial pneumonitis. Chronic disease manifestations reflect the organ system affected. Diagnosis is confirmed by several serologic techniques, isolation of the organism, or PCR. Treatment is with doxycycline or chloramphenicol.

Coxiella burnetii is a small, intracellular, pleomorphic bacillus that is no longer classified as *Rickettsia*. Molecular studies have reclassified it as Proteobacteria in the same group as *Legionella* sp.

Q fever can be acute or chronic. Acute disease causes a febrile illness that often affects the respiratory system, although sometimes the liver is involved. Chronic Q fever usually manifests as endocarditis or hepatitis; osteomyelitis may occur.

Worldwide in its distribution, Q fever is maintained as an inapparent infection in domestic or farm animals. Sheep, cattle, and goats are the principal reservoirs for human infection. *C. burnetii* persists in stool, urine, milk, and tissues (especially the placenta), so that fomites and infective aerosols form easily. *C. burnetii* is also maintained in nature through an animal-tick cycle.

Etiology

Cases occur among workers whose occupations bring them in close contact with farm animals or their products. Transmission is usually by inhalation of infected aerosols, but the disease can also be contracted by ingesting infective raw milk. *C. burnetii* is very virulent, resists inactivation, and remains viable in dust and stool for months; even a single organism can cause infection. Very rarely, the disease is transmitted from person to person.

Symptoms and Signs

The incubation period averages 18 to 21 days (range 9 to 28 days). Some infections are minimally symptomatic; however, most patients have influenza-like symptoms. Onset is abrupt, with fever, severe headache, chills, severe malaise, myalgia, anorexia, and sweats. Fever may rise to 40° C and persist 1 to > 3 wk. Respiratory symptoms (a dry nonproductive cough, pleuritic chest pain) appear 4 to 5 days after onset of illness. These symptoms may be particularly severe in elderly or debilitated patients. During examination, lung crackles are commonly noted, and findings suggesting consolidation may be present. Unlike rickettsial diseases, acute Q fever does not cause a rash.

Acute hepatic involvement, occurring in some patients, resembles viral hepatitis, with fever, malaise, hepatomegaly with right upper abdominal pain, and possibly jaundice. Headache and respiratory signs are frequently absent. Chronic Q fever hepatitis may manifest as FUO. Liver biopsy may show granulomas, which should be differentiated from other causes of liver granulomas (eg, TB, sarcoidosis, histoplasmosis, brucellosis, tularemia, syphilis).

Endocarditis resembles viridans group subacute bacterial endocarditis (see p.); the aortic valve is most commonly affected, but vegetations may occur on any valve. Marked finger clubbing, arterial emboli, hepatomegaly, splenomegaly, and a purpuric rash may occur.

The mortality rate is only 1% of untreated patients but is higher in those with endocarditis. Some patients with neurologic involvement have residual impairment.

Diagnosis

• Immunofluorescence assay of infected tissue

Symptoms do not readily suggest the diagnosis. Early on, Q fever resembles many infections (eg, influenza, other viral infections, salmonellosis, malaria, hepatitis, brucellosis). Later, it resembles many forms of bacterial, viral, and mycoplasmal pneumonias. Contact with animals or animal products is an important clue.

Immunofluorescence assay (IFA) of infected tissue is the diagnostic method of choice; alternatively, enzyme-linked immunosorbent assay (ELISA) may be done. Acute and convalescent serum specimens (typically complement fixation) may be used. PCR can identify the organism in biopsy specimens. *C. burnetii* may be isolated from clinical specimens, but only by special research laboratories; routine blood and sputum cultures are negative.

Patients with respiratory symptoms or signs require chest x-ray; findings may include atelectasis, pleural-based opacities, pleural effusion, and lobar consolidation. The gross appearance of the lungs may resemble bacterial pneumonia but, histologically, more closely resembles psittacosis and some viral pneumonias.

In acute Q fever, CBC may be normal, but about 30% of patients have an elevated WBC count. Alkaline phosphatase, AST, and ALT levels are mildly elevated to 2 to 3 times the normal level in typical cases. If obtained, liver biopsy specimens often show diffuse granulomatous changes.

Treatment

• Doxycycline

Primary treatment is doxycycline 200 mg po once followed by 100 mg po bid until the patient improves, has been afebrile for about 5 days, and has received treatment for at least 7 days. Chloramphenicol 500 mg po or IV qid for 7 days is 2nd-line treatment. Fluoroquinolones and macrolides are also effective.

For endocarditis, treatment needs to be prolonged (months to years to lifelong). Clinical signs, ESR, blood count, and antibody titers should be monitored to determine when to stop treatment. A tetracycline plus rifampin or ciprofloxacin is usually preferred. Some experts use hydroxychloroquine as an additional drug. When antibiotic treatment is only partially effective, damaged valves must be replaced surgically, although some cures have occurred without surgery. Clear-cut regimens for chronic hepatitis have not been determined.

Prevention

Vaccines are effective and should be used to protect slaughterhouse and dairy workers, rendering-plant workers, herders, woolsorters, farmers, and other people at risk. These vaccines are not available commercially but may be obtained from special laboratories (eg, the US Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland).

Chapter 140. Anaerobic Bacteria

Introduction

Bacteria can be classified by their need and tolerance for O_2:

• Facultative bacteria, which grow in the presence or absence of O_2

• Microaerophilic bacteria, which tolerate low O_2 concentrations but grow better anaerobically or with > 10% CO_2

• Obligate anaerobic bacteria, which are intolerant of O_2

Obligate anaerobes replicate at sites with low oxidation-reduction potential (eg, necrotic, devascularized tissue). Obligate anaerobes have been categorized based on their O_2 tolerance: strict anaerobes grow in ≤ 0.4% O_2; moderate anaerobes grow in 0.8 to 2.5% O_2; and aerotolerant anaerobes grow in ≥ 2.5% O_2. The obligate anaerobes that commonly cause infection can tolerate atmospheric O_2 for at least 8 h and frequently for up to 72 h.

Obligate anaerobes are major components of the normal microflora on mucous membranes, especially of the mouth, lower GI tract, and vagina; these anaerobes cause disease when normal mucosal barriers break down.

Gram-negative anaerobes and some of the infections they cause include

• *Bacteroides* (most common): Intra-abdominal infections

• *Fusobacterium:* Abscesses, wound infections, and pulmonary and intracranial infections

• *Porphyromonas:* Aspiration pneumonia and periodontitis

• *Prevotella:* Intra-abdominal and soft-tissue infections

Gram-positive anaerobes and some of the infections they cause include

• *Actinomyces:* Head, neck, abdominal, and pelvic infections and aspiration pneumonia

• *Clostridium:* Gas gangrene due to *C. perfringens*, food poisoning due to *C. perfringens type A*, botulism due to *C. botulinum*, tetanus due to *C. tetani*, and *C. difficile*-induced diarrhea (pseudomembranous colitis)

• *Peptostreptococcus:* Oral, respiratory, and intra-abdominal infections

• *Propionibacterium:* Foreign body infections (eg, in a cerebrospinal fluid shunt, prosthetic joint, or cardiac device)

Anaerobic infections are typically suppurative, causing abscess formation and tissue necrosis (often the result of thrombophlebitis, gas formation, or both). Many anaerobes produce tissue-destructive enzymes as well as some of the most potent paralytic toxins known.

Clues to anaerobic infection include

• Polymicrobial results on Gram stain or culture

• Gas in pus or infected tissues

• Foul odor of pus or infected tissues

• Necrotic infected tissues

• Site of infection near mucosa where anaerobic microflora normally reside

Testing: Specimens for anaerobic culture should be obtained by aspiration or biopsy from normally sterile sites. Delivery to the laboratory should be prompt, and transport devices should provide an O_2-free atmosphere of carbon dioxide, hydrogen, and nitrogen. Swabs are best transported in an anaerobically sterilized, semisolid medium such as Cary-Blair transport medium.

Clostridia

Clostridia are spore-forming, gram-positive bacilli present widely in dust, soil, and vegetation and as normal flora in mammalian GI tracts.

Nearly 100 *Clostridium* sp have been identified, but only 25 to 30 commonly cause human or animal disease.

Pathophysiology

The pathogenic species produce tissue-destructive and neural exotoxins that are responsible for disease manifestations. Clostridia may become pathogenic when tissue O_2 tension and pH are low. Such an anaerobic environment may develop in ischemic or devitalized tissue, as occurs in primary arterial insufficiency or after severe penetrating or crushing injuries. The deeper and more severe the wound, the more prone the patient is to clostridial infection, especially if there is even minimal contamination by foreign matter. Clostridial disease can also occur after injection of street drugs. Serious noninfectious disease can occur after ingestion of home-canned foods in which clostridia have produced toxins.

Diseases Caused by Clostridia

Diseases caused by clostridia include

• Botulism (due to *C. botulinum*)

• *C. difficile*-induced colitis

• Gastroenteritis

• Soft-tissue infections

• Tetanus (due to *C. tetani*)

• Enteritis necroticans (due to *C. perfringens type C*)

• Neutropenic enterocolitis (due to *C. septicum*)

The most frequent clostridial infection is minor, self-limited gastroenteritis, typically due to *C. perfringens type A*. Serious clostridial diseases are relatively rare but can be fatal. Abdominal disorders, such as cholecystitis, peritonitis, ruptured appendix, and bowel perforation can involve *C. perfringens, C. ramosum*, and many others. Muscle necrosis and soft-tissue infection, which is characterized by crepitant cellulitis, myositis, and clostridial myonecrosis, can be caused by *C. perfringens*. Tissue necrosis can be caused by *C. septicum*. Clostridia also appear as components of mixed flora in common mild wound infections; their role in such infections is unclear.

Hospital-acquired clostridial infection is increasing, particularly in postoperative and immunocompromised patients. Severe clostridial sepsis may complicate intestinal perforation and obstruction.

Actinomycosis

Actinomycosis is a chronic localized or hematogenous infection caused by *Actinomyces israelii*. Symptoms are a local abscess with multiple draining sinuses, a TB-like pneumonitis, and low-grade septicemia. Diagnosis is by the typical appearance plus laboratory identification. Treatment is with a long course of antibiotics and surgery.

The causative organisms, *Actinomyces* sp (most commonly *A. israelii*), are often present commensally on the gums, tonsils, and teeth. However, many, if not most, infections are polymicrobial, with other bacteria (oral anaerobes, staphylococci, streptococci, *Aggregatibacter* [previously *Actinobacillus*] *actinomycetemcomitans*, Enterobacteriaceae) frequently cultured from lesions.

Actinomycosis most often occurs in adult males and takes several forms:

• Cervicofacial (lumpy jaw): The most common portal of entry is decayed teeth.

• Thoracic: Pulmonary disease results from aspiration of oral secretions.

• Abdominal: Disease presumably results from a break in the mucosa of a diverticulum or the appendix or from trauma.

• Uterine: This localized pelvic form is a complication of certain types of intrauterine device (IUD).

• Generalized: Rarely, the infection spreads from primary sites, presumably by hematogenous seeding.

Symptoms and Signs

The characteristic lesion is an indurated area of multiple, small, communicating abscesses surrounded by granulation tissue. Lesions tend to form sinus tracts that communicate to the skin and drain a purulent discharge containing "sulfur" granules (rounded or spherical, usually yellowish, and ≤ 1 mm in diameter). Infection spreads to contiguous tissues, but only rarely hematogenously.

The **cervicofacial form** usually begins as a small, flat, hard swelling, with or without pain, under the oral mucosa or the skin of the neck or as a subperiosteal swelling of the jaw. Subsequently, areas of softening appear and develop into sinuses and fistulas that discharge the characteristic sulfur granules. The cheek, tongue, pharynx, salivary glands, cranial bones, meninges, or brain may be affected, usually by direct extension.

In the **abdominal form**, the intestines (usually the cecum and appendix) and the peritoneum are infected. Pain, fever, vomiting, diarrhea or constipation, and emaciation are characteristic. One or more abdominal masses develop and cause signs of partial intestinal obstruction. Draining sinuses and intestinal fistulas may develop and extend to the external abdominal wall.

In the **localized pelvic form**, patients who use an IUD have vaginal discharge and pelvic or lower abdominal pain.

In the **thoracic form**, lung involvement resembles TB. Extensive invasion may occur before chest pain, fever, and productive cough appear. Perforation of the chest wall, with chronic draining sinuses, may result.

In the **generalized form**, infection spreads hematogenously to multiple areas, including the skin, vertebral bodies, brain, liver, kidneys, ureters, and, in women, pelvic organs. Diverse symptoms (eg, back pain, headache, abdominal pain) related to these sites may occur.

Diagnosis

• Microscopy

• Culture

Diagnosis is suspected clinically and by x-ray. It is confirmed by identification of *A. israelii* in sputum, pus, or a biopsy specimen by microscopy and by culture.

In pus or tissue, the microorganism appears as the distinctive sulfur granules or as tangled masses of branched and unbranched wavy bacterial filaments, pus cells, and debris, surrounded by an outer zone of radiating, club-shaped, hyaline, and refractive filaments that take hematoxylin-eosin stain in tissue but are positive on Gram stain.

Lesions in any location may simulate malignant growths. Lung lesions must be distinguished from those of TB and cancer. Most abdominal lesions occur in the ileocecal region and are difficult to diagnose, except during laparotomy or when draining sinuses appear in the abdominal wall. Aspiration liver biopsy should be avoided because it can cause a persistent sinus.

Prognosis

The disease is slowly progressive. Prognosis relates directly to early diagnosis and is most favorable in the cervicofacial form and progressively worse in the thoracic, abdominal, and generalized forms, especially if the CNS is involved.

Treatment

• High-dose penicillin

Most patients respond to antibiotics, although response is usually slow because of extensive tissue induration and the relatively avascular nature of the lesions. Therefore, treatment must be continued for at least 8 wk and occasionally for ≥ 1 yr, until symptoms and signs have resolved.

High doses of penicillin G (eg, 3 to 5 million units IV q 6 h) are usually effective. Penicillin V 1 g po qid may be substituted after about 2 to 6 wk. Tetracycline 500 mg po q 6 h may be given instead of penicillin. Minocycline, clindamycin, and erythromycin have also been successful. Antibiotic regimens may be broadened to cover other pathogens cultured from lesions.

Anecdotal reports suggest that hyperbaric O_2 therapy is helpful.

Extensive and repeated surgical procedures may be required. Sometimes small abscesses can be aspirated; large ones are drained, and fistulas are excised surgically.

Botulism

Botulism is neuromuscular poisoning due to *Clostridium botulinum* toxin. Botulism may occur without infection if toxin is ingested. Symptoms are symmetric cranial nerve palsies accompanied by a symmetric descending weakness and flaccid paralysis without sensory deficits. Diagnosis is clinical and by laboratory identification of toxin. Treatment is with support and antitoxin.

C. botulinum elaborates 7 types of antigenically distinct neurotoxins, which interfere with release of acetylcholine at peripheral nerve endings. Four of the toxins (types A, B, E, and rarely F) affect humans. Types A and B are highly poisonous proteins resistant to digestion by GI enzymes. About 50% of food-borne outbreaks in the US are caused by type A toxin, followed by types B and E. Type A toxin occurs predominantly west of the Mississippi River, type B in the eastern states, and type E in Alaska and the Great Lakes area (type E is frequently associated with ingestion of fish products). Type A toxin is used therapeutically to relieve excess muscle activity; botulinum toxin has also been developed as a bioweapon.

Botulism occurs in 3 forms:

• Food-borne

• Wound

• Infant

In food-borne botulism, neurotoxin produced in contaminated food is eaten. Neurotoxin is elaborated in vivo by *C. botulinum* in infected tissue in wound botulism and in the large intestine in infant botulism (see p.).

C. botulinum spores are highly heat-resistant and may survive boiling for several hours at 100° C. However, exposure to moist heat at 120° C for 30 min kills the spores. Toxins, on the other hand, are readily destroyed by heat, and cooking food at 80° C for 30 min safeguards against botulism. Toxin production (especially type E) can occur at temperatures as low as 3° C (ie, inside a refrigerator) and does not require strict anaerobic conditions.

Sources of infection: Home-canned foods, particularly low-acid foods, are the most common sources, but commercially prepared foods have been implicated in about 10% of outbreaks. Vegetables, fish, fruits, and condiments are the most common vehicles, but beef, milk products, pork, poultry, and other foods have been involved. Of outbreaks caused by seafood, type E causes about 50%; types A and B cause the rest. In recent years, foods that are not canned (eg, foil-wrapped baked potatoes, chopped garlic in oil, patty melt sandwiches) have caused restaurant-associated outbreaks.

C. botulinum spores are common in the environment, and many cases may be caused by ingestion or inhalation of dust or by absorption through the eyes or a break in the skin.

Injecting drugs with unsterilized needles can cause wound botulism. Injecting contaminated heroin into a muscle or under the skin (skin popping) is riskiest.

Symptoms and Signs

Food-borne botulism: Symptoms begin abruptly, usually 18 to 36 h after toxin ingestion, although the incubation period may vary from 4 h to 8 days. Nausea, vomiting, abdominal cramps, and diarrhea frequently precede neurologic symptoms. Neurologic symptoms are characteristically bilateral and symmetric, beginning with the cranial nerves and followed by descending weakness or paralysis. There are no sensory disturbances, and the sensorium usually remains clear.

Common initial symptoms and signs include dry mouth, blurred or double vision, drooping eyelids, slurred speech, and difficulty swallowing. Pupillary light reflex is diminished or totally lost. Dysphagia can lead to aspiration pneumonia. Muscles of respiration and of the extremities and trunk progressively weaken in a descending pattern. Fever is absent, and the pulse remains normal or slow unless intercurrent infection develops. Constipation is common after neurologic impairment appears. Major complications include respiratory failure caused by diaphragmatic paralysis and pulmonary infections.

Wound botulism: Neurologic symptoms appear, as in food-borne botulism, but there are no GI symptoms or evidence implicating food as a cause. A history of a traumatic injury or a deep puncture wound in the preceding 2 wk may suggest the diagnosis. A thorough search should be made for breaks in the skin and for skin abscesses caused by self-injection of illegal drugs.

Diagnosis

• Toxin assays

• Sometimes electromyography

Botulism may be confused with Guillain-Barre syndrome, poliomyelitis, stroke, myasthenia gravis, tick paralysis, and poisoning caused by curare or belladonna alkaloids. Electromyography shows

characteristic augmented response to rapid repetitive stimulation in most cases.

In **food-borne botulism**, the pattern of neuromuscular disturbances and ingestion of a likely food source are important diagnostic clues. The simultaneous presentation of at least 2 patients who ate the same food simplifies diagnosis, which is confirmed by demonstrating *C. botulinum* toxin in serum or stool or by isolating the organism from stool. Finding *C. botulinum* toxin in suspect food identifies the source.

In **wound botulism**, finding toxin in serum or isolating *C. botulinum* organisms on anaerobic culture of the wound confirms the diagnosis.

Toxin assays are done only by certain laboratories, which may be located through local health authorities or the Centers for Disease Control and Prevention (CDC).

Treatment

• Supportive care

• Equine trivalent antitoxin

Anyone known or thought to have been exposed to contaminated food must be carefully observed. Administration of activated charcoal may be helpful. Patients with significant symptoms often have impaired airway reflexes, so if charcoal is used, it should be given via gastric tube, and the airway should be protected by a cuffed endotracheal tube.

The greatest threat to life is respiratory impairment and its complications. Patients should be hospitalized and closely monitored with serial measurements of vital capacity. Progressive paralysis prevents patients from showing signs of respiratory distress as their vital capacity decreases. Respiratory impairment requires management in an ICU, where intubation and mechanical ventilation are readily available. Improvements in such supportive care have reduced the mortality rate to < 10%.

Nasogastric intubation is the preferred method of alimentation because it simplifies management of calories and fluids, stimulates intestinal peristalsis (which eliminates *C. botulinum* from the gut), allows the use of breast milk in infants, and avoids the potential infectious and vascular complications inherent in IV alimentation.

Patients with wound botulism require wound debridement and parenteral antibiotics such as penicillin or metronidazole.

Antitoxin: Trivalent equine antitoxin (A, B, E) is available from the CDC through state health departments. Antitoxin does not inactivate toxin that is already bound at the neuromuscular junction; therefore, preexisting neurologic impairment cannot be reversed rapidly. (Ultimate recovery depends on regeneration of nerve endings, which may take weeks or months.) However, antitoxin may slow or halt further progression. In patients with wound botulism, antitoxin can reduce complications and mortality rate. Antitoxin should be given as soon as possible after clinical diagnosis and not delayed to await culture results. Antitoxin is less likely to be of benefit if given > 72 h after symptom onset.

In the US, botulism equine trivalent antitoxin is given as a single 10-mL dose containing 7500 IU of antitoxin A, 5500 IU of antitoxin B, and 8500 IU of antitoxin E. All patients who require the antitoxin must be reported to state health authorities or the CDC. Antitoxin is available only through the CDC, the telephone number is 404-639-2206 weekdays and 404-639-2888 for all other times. Because antitoxin is derived from horse serum, there is a risk of anaphylaxis or serum sickness. (For precautions, see Drug Hypersensitivity on p. ; for treatment, see Anaphylaxis on p. .)

Prevention

Because even minute amounts of *C. botulinum* toxin can cause serious illness, all materials suspected of containing toxin require special handling. Toxoids are available for active immunization of people working

with *C. botulinum* or its toxins. Details regarding specimen collection and handling can be obtained from state health departments or the CDC.

Correct canning and adequate heating of home-canned food before serving are essential. Canned foods showing evidence of spoilage and swollen or leaking cans should be discarded.

Infant Botulism

Infant botulism results from ingestion of *C. botulinum* spores, their colonization of the large intestine, and toxin production in vivo.

Infant botulism occurs most often in infants < 6 mo. The youngest reported patient was 2 wk, and the oldest was 12 mo. Unlike food-borne botulism, infant botulism is not caused by ingestion of a preformed toxin. Most cases are idiopathic, although some have been traced to ingestion of honey, which may contain *C. botulinum* spores; thus, infants < 12 mo should not be fed honey.

Symptoms and Signs

Constipation is present initially in 90% of cases and is followed by neuromuscular paralysis, beginning with the cranial nerves and proceeding to peripheral and respiratory musculature. Cranial nerve deficits typically include ptosis, extraocular muscle palsies, weak cry, poor suck, decreased gag reflex, pooling of oral secretions, poor muscle tone (floppy baby syndrome), and an expressionless face. Severity varies from mild lethargy and slowed feeding to severe hypotonia and respiratory insufficiency.

Diagnosis

Infant botulism may be confused with sepsis, congenital muscular dystrophy, spinal muscular atrophy, hypothyroidism, and benign congenital hypotonia. Finding *C. botulinum* toxin or organisms in the stool establishes the diagnosis.

Treatment

• Human botulism antitoxin

Infants are hospitalized, and supportive care (eg, ventilatory support) is given as needed.

Specific treatment is with human botulism immune globulin. Treatment is started as soon as the diagnosis is suspected; waiting for confirmatory test results is dangerous. The dose is 50 mg/kg IV once, given slowly. The horse serum antitoxin used in adults is not recommended for infants.

Antibiotics are not given because they may lyse *C. botulinum* in the gut and increase toxin availability.

Clostridium Difficile-Induced Diarrhea

(Pseudomembranous Colitis)

Toxins produced by *Clostridium difficile* strains in the GI tract cause pseudomembranous colitis, typically after antibiotic use. Symptoms are diarrhea, sometimes bloody, rarely progressing to sepsis and acute abdomen. Diagnosis is by identifying *C. difficile* toxin in stool. Treatment is with oral metronidazole or vancomycin.

C. difficile is the most common cause of antibiotic-associated colitis and is typically hospital-acquired. *C. difficile*-induced diarrhea occurs in up to 8% of hospitalized patients and is responsible for 20 to 30% of cases of hospital-acquired diarrhea. Extremes of age, severe underlying disease, prolonged hospital stay, and living in a nursing home are risk factors.

C. difficile is carried asymptomatically by 15 to 70% of neonates, 3 to 8% of healthy adults, and perhaps 20% of hospitalized adults (more in long-term care facilities) and is common in the environment (eg, soil,

water, household pets). Disease may result from overgrowth of intrinsic organisms or infection from an external source. Health care workers are frequently the source of transmission.

Recently, a more virulent strain, BI/NAP1/027, has become prominent in hospital out-breaks. This strain produces substantially more toxin, causes more severe illness with greater chance of relapse, is more transmissible, and responds less well to antibiotic treatment.

Pathophysiology

Antibiotic-induced changes in GI flora are the dominant predisposing factor. Although most antibiotics have been implicated, cephalosporins (particularly 3rd-generation), penicillins (particularly ampicillin and amoxicillin), clindamycin, and fluoroquinolones pose the highest risk. *C. difficile*-induced colitis may also follow use of certain antineoplastic drugs.

The organism secretes both a cytotoxin and an enterotoxin. The main effect is on the colon, which secretes fluid and develops characteristic pseudomembranes—discrete yellow-white plaques that are easily dislodged. Plaques may coalesce in severe cases. Toxic megacolon, which rarely develops, is somewhat more likely after use of antimotility drugs. Limited tissue dissemination occurs very rarely, as do sepsis and acute abdomen. Reactive arthritis has occurred after *C. difficile*-induced diarrhea.

Symptoms and Signs

Symptoms typically begin 5 to 10 days after starting antibiotics but may occur on the first day or up to 2 mo later. Diarrhea may be mild and semiformed or frequent and watery. Cramping or pain is common, but nausea and vomiting are rare. The abdomen may be slightly tender.

Patients with significant colitis or toxic megacolon have more pain and appear very ill, with tachycardia and abdominal distention and tenderness. Peritoneal signs are present in those with perforation.

Diagnosis

• Stool assay for toxin

• Sometimes sigmoidoscopy

Diagnosis should be suspected in any patient who develops diarrhea within 2 mo of antibiotic use or 72 h of hospital admission. Diagnosis is confirmed by stool (sample, not swab) assay for *C. difficile* toxin. A new real-time PCR test for the toxin gene *tcdB* may be superior to current assays. A single sample is usually adequate, but repeat samples should be submitted when suspicion is high and the first sample is negative. Fecal leukocytes are often present but not specific.

Sigmoidoscopy, which can confirm the presence of pseudomembranes, should be done if patients have ileus or if toxin assays are non-diagnostic. Abdominal x-rays, CT, or both are usually done if fulminant colitis, perforation, or megacolon is suspected.

Treatment

• Oral metronidazole or vancomycin

Metronidazole 250 mg po q 6 h or 500 mg po q 8 h for 10 days is the therapy of choice. If patients do not respond within 48 h, vancomycin 125 to 500 mg po q 6 h for 10 days may be given. Some patients require bacitracin 500 mg po q 6 h for 10 days, cholestyramine resin, or *Saccharomyces boulardii* yeast. Relapses occur in 15 to 20% of patients. Nitazoxanide 500 mg po q 12 h appears to be comparable to oral vancomycin 125 mg but is not commonly used in the US. A few patients require total colectomy for cure.

Infection control measures are vital to reduce the spread of *C. difficile* among patients and health care workers.

Clostridial Intra-Abdominal Infections

Clostridia, primarily *Clostridium perfringens*, are common in mixed intra-abdominal infections due to a ruptured viscus or pelvic inflammatory disease.

Clostridium sp are common residents of the GI tract and are present in many abdominal infections, generally mixed with other enteric organisms. Clostridia are often the primary agents in emphysematous cholecystitis, gas gangrene of the uterus (previously common with septic abortion), certain other female genital tract infections (tubo-ovarian, pelvic, and uterine abscesses), and infection after perforation in colon carcinoma.

The primary organisms are *C. perfringens* and, in the case of colon carcinoma, *C. septicum*. The organism produces exotoxins (lecithinases, hemolysins, collagenases, proteases, lipases) that can cause suppuration. Gas formation is common. Clostridial septicemia may cause hemolytic anemia because lecithinase disrupts RBC membranes. With severe hemolysis and coexisting toxicity, acute renal failure can occur.

Symptoms are similar to those of other abdominal infections (eg, pain, fever, abdominal tenderness, a toxic appearance). In uterine infection, gas sometimes escapes through the cervix. Rarely, acute tubular necrosis develops.

Diagnosis

• Gram stain and culture

Early diagnosis requires a high index of suspicion. Early and repeated Gram stains and cultures of the site, pus, lochia, and blood are indicated. Because *C. perfringens* can occasionally be isolated from healthy vagina and lochia, cultures are not specific. X-rays may show local gas production (eg, in the biliary tree, gallbladder wall, or uterus).

Treatment

• Surgical debridement

• High-dose penicillin

Treatment is surgical debridement and penicillin G 5 million units IV q 6 h for at least 1 wk. Organ removal (eg, hysterectomy) may be necessary and can be lifesaving if debridement is insufficient. If acute tubular necrosis develops, dialysis is needed. The usefulness of hyperbaric O_2 has not been established.

Clostridial Necrotizing Enteritis

(Enteritis Necroticans; Pigbel)

Clostridial necrotizing enteritis is necrotizing inflammation of the jejunum and ileum caused by *Clostridium perfringens*.

C. perfringens occasionally causes severe inflammatory disease in the small bowel (primarily, the jejunum). Inflammation is segmental, involving small or large patches with varying degrees of hemorrhage and necrosis. Perforation may occur.

Disease is caused by clostridial β-toxin, which is very sensitive to proteolytic enzymes and is inactivated by normal cooking. Disease occurs primarily in populations with multiple risk factors, including protein deprivation (causing inadequate synthesis of protease enzymes), poor food hygiene, episodic meat feasting, staple diets containing trypsin inhibitors (eg, sweet potatoes), and *Ascaris* infestation (these parasites secrete a trypsin inhibitor). These factors are typically present collectively only in the hinterlands of New Guinea and parts of Africa, Central and South America, and Asia. In New Guinea, the

disease is known as pigbel and is usually spread through contaminated pork, other meats, and perhaps peanuts.

Severity varies from mild diarrhea to a fulminant course of severe abdominal pain, vomiting, bloody stool, and sometimes death within 24 h.

Treatment is with antibiotics (penicillin G, metronidazole). Perhaps 50% of seriously ill patients require surgery for perforation, persistent intestinal obstruction, or failure to respond to antibiotics. An experimental toxoid vaccine has been used successfully in endemic areas but is not available commercially.

Neutropenic enterocolitis (typhlitis): This similar syndrome develops in the cecum of neutropenic patients (eg, those with leukemia or receiving cancer chemotherapy). It may be associated with sepsis due to *Clostridium septicum*. Symptoms are fever, abdominal pain, and diarrhea.

Treatment is with antibiotics, but surgery may be necessary.

Neonatal necrotizing enterocolitis: Neonatal necrotizing enterocolitis (see p.), which occurs in neonatal ICUs, may be caused by *C. perfringens, C. butyricum*, or *C. difficile*, although the role of these organisms needs further study.

Clostridium perfringens Food Poisoning

***Clostridium perfringens* food poisoning is acute gastroenteritis caused by ingestion of contaminated food.**

C. perfringens is widely distributed in feces, soil, air, and water. Contaminated meat has caused many outbreaks. When meat contaminated with *C. perfringens* is left at room temperature, the organism multiplies and produces toxin. Outbreaks typically occur in commercial establishments and rarely at home. Once inside the GI tract, *C. perfringens* produces an enterotoxin that acts on the small bowel. Only *C. perfringens type A* has been definitively linked to this food poisoning syndrome. The enterotoxin produced is sensitive to heat (> 75° C).

Mild gastroenteritis is most common, with onset of symptoms 6 to 24 h after ingestion of contaminated food. The most common symptoms are watery diarrhea and abdominal cramps. Vomiting is unusual. Symptoms typically resolve within 24 h; severe or fatal cases rarely occur.

Diagnosis is based on epidemiologic evidence and isolation of large numbers of organisms from contaminated food or from stools of affected people or on direct identification of enterotoxin in stool samples.

To prevent disease, people should promptly refrigerate leftover cooked meat and reheat it thoroughly (internal temperature, 75° C) before serving.

Treatment is supportive (see p.); antibiotics are not given.

Clostridial Soft-Tissue Infections

Clostridial soft-tissue infections include cellulitis, myositis, and clostridial myonecrosis. They usually occur after trauma. Symptoms may include edema, pain, gas with crepitation, foul-smelling exudates, intense coloration of the site, and progression to shock and renal failure. Diagnosis is by inspection and smell, confirmed by culture. Treatment is with penicillin and surgical debridement. Hyperbaric O$_2$ is sometimes beneficial.

Clostridium perfringens is the most common species involved. Infection develops hours or days after injury, usually in an extremity after severe crushing or penetrating trauma devitalizes tissue, creating anaerobic conditions. The presence of foreign material (even if sterile) markedly increases risk of

clostridial infection. Infection may also occur in operative wounds, particularly in patients with underlying occlusive vascular disease. Rarely, spontaneous cases occur, usually involving *C. septicum* originating from occult colon perforation in patients with colon cancer, diverticulitis, or bowel ischemia. Infection typically results in gas collection in soft tissues.

In suitable conditions (low oxidation-reduction potential, low pH), as occur in devitalized tissue, infection progresses rapidly, from initial injury through shock, toxic delirium, and death within as little as 1 day.

Symptoms and Signs

Clostridial cellulitis occurs as a localized infection in a superficial wound, usually ≥ 3 days after injury. Infection may spread extensively along fascial planes, often with evident crepitation and abundant gas bubbling, but toxicity is much less severe than with extensive myonecrosis, and pain is minimal. Bullae are frequently evident, with foul-smelling, serous, brown exudate. Discoloration and gross edema of the extremity are rare. Clostridial skin infections associated with primary vascular occlusion of an extremity rarely progress to severe toxic myonecrosis or extend beyond the line of demarcation.

Clostridial myositis (suppurative infection of muscle without necrosis) is most common among parenteral drug users. It resembles staphylococcal pyomyositis and lacks the systemic symptoms of clostridial myonecrosis. Edema, pain, and frequently gas in the tissues occur. The infection spreads rapidly and may progress to myonecrosis.

In **clostridial myonecrosis** (gas gangrene), initial severe pain is common, sometimes even before other findings. The wound site may be pale initially, but it becomes red or bronze, often with blebs or bullae, and finally turns blackish green. The area is tensely edematous and tender to palpation. Crepitation is less obvious early than it is in clostridial cellulitis but is ultimately palpable in about 80%. Wounds and drainage have a particularly foul odor.

With progression, patients appear toxic, with tachycardia, pallor, and hypotension. Shock and renal failure occur, although patients often remain alert until the terminal stage. Unlike clostridial uterine infection, overt hemolysis is rare in gas gangrene of the extremities, even in terminally ill patients. Whenever massive hemolysis occurs, mortality of 70 to 100%, due to acute renal failure and septicemia, can be expected.

Diagnosis

• Clinical evaluation

• Gram stain and culture

Early suspicion and intervention are essential; clostridial cellulitis responds well to treatment, but myonecrosis has a mortality rate of ≥ 40% with treatment and 100% without treatment.

Although localized cellulitis, myositis, and spreading myonecrosis may be clinically distinct, differentiation often requires surgical exploration. In myonecrosis, muscle tissue is visibly necrotic; the affected muscle is a lusterless pink, then deep red, and finally gray-green or mottled purple and does not contract with stimulation. X-rays may show local gas production, and CT and MRI delineate the extent of gas and necrosis.

Wound exudate should be cultured for anaerobic and aerobic organisms. Because of their short generation time, anaerobic cultures of *Clostridia* may be positive in as little as 6 h. However, other anaerobic and aerobic bacteria, including members of the Enterobacteriaceae family and *Bacteroides, Streptococcus*, and *Staphylococcus* spp, alone or mixed, can cause severe clostridia-like cellulitis, extensive fasciitis, or myonecrosis (see Necrotizing Sub-cutaneous Infection on p. 700). Also, many wounds, particularly if open, are contaminated with both pathogenic and nonpathogenic clostridia that are not responsible for the infection.

The presence of clostridia is significant when

• Gram stain shows them in large numbers.

• Few PMNs are found in the exudates.

• Free fat globules are demonstrated with Sudan stain.

However, if PMNs are abundant and the smear shows many chains of cocci, an anaerobic streptococcal or staphylococcal infection should be suspected. Abundant gram-negative bacilli may indicate infection with one of the Enterobacteriaceae or a *Bacteroides* sp (see also). Detection of clostridial toxins in the wound or blood is useful only in the rare case of wound botulism (see).

Treatment

• Drainage and debridement

• Penicillin plus clindamycin

When clinical signs of clostridial infection (eg, gas, myonecrosis) are present, rapid, aggressive intervention is mandatory. Thorough drainage and debridement are as important as antibiotics; both should be instituted rapidly. Penicillin G is the drug of choice; 1 to 2 million units IV q 2 to 3 h should be given immediately for severe cellulitis and myonecrosis. Addition of clindamycin 600 mg IV q 6 h is beneficial. If gram-negative organisms are seen or suspected, a broad-spectrum antibiotic (eg, ticarcillin plus clavulanate, ampicillin plus sulbactam, piperacillin plus tazobactam) should be added.

Hyperbaric O_2 therapy may be helpful in extensive myonecrosis, particularly in the extremities, as a supplement to antibiotics and surgery. Hyperbaric O_2 therapy may salvage tissue and lessen mortality and morbidity if it is started early, *but it should not delay surgical debridement.*

Tetanus

(Lockjaw)

Tetanus is acute poisoning from a neurotoxin produced by *Clostridium tetani*. Symptoms are intermittent tonic spasms of voluntary muscles. Spasm of the masseters accounts for the name lockjaw. Diagnosis is clinical. Treatment is with immune globulin and intensive support.

Tetanus bacilli form durable spores that occur in soil and animal feces and remain viable for years. Worldwide, tetanus is estimated to cause over half a million deaths annually, mostly in neonates and young children, but the disease is so rarely reported that all figures are only rough estimates. In the US, only 37 cases were reported in 2001. Disease incidence is directly related to the immunization level in a population, attesting to the effectiveness of preventive efforts. In the US, well over half of elderly patients have inadequate antibody levels and account for one third to one half of cases. Most of the rest occur in inadequately immunized patients aged 20 to 59. Patients < 20 account for < 10%. Patients with burns, surgical wounds, or a history of injection drug abuse are especially prone to developing tetanus. However, tetanus may follow trivial or even inapparent wounds. Infection may also develop postpartum in the uterus (maternal tetanus) and in a neonate's umbilicus (tetanus neonatorum).

Pathophysiology

Manifestations of tetanus are caused by an exotoxin (tetanospasmin). The toxin may enter the CNS along the peripheral motor nerves or may be bloodborne to nervous tissue. Tetanospasmin binds irreversibly to the ganglioside membranes of nerve synapses, blocking release of inhibitory transmitter from nerve terminals and thereby causing a generalized tonic spasticity, usually with superimposed intermittent tonic seizures. Disinhibition of autonomic neurons and loss of control of adrenal catecholamine release cause autonomic instability and a hypersympathetic state. Once bound, the toxin cannot be neutralized.

Most often, tetanus is generalized, affecting skeletal muscles throughout the body. However, tetanus is sometimes localized to muscles near an entry wound.

Symptoms and Signs

The incubation period ranges from 2 to 50 days (average, 5 to 10 days). Symptoms include

• Jaw stiffness (most frequent)

• Difficulty swallowing

• Restlessness

• Irritability

• Stiff neck, arms, or legs

• Headache

• Sore throat

• Tonic spasms

Later, patients have difficulty opening their jaw (trismus).

Spasms: Facial muscle spasm produces a characteristic expression with a fixed smile and elevated eyebrows (risus sardonicus). Rigidity or spasm of abdominal, neck, and back muscles—even opisthotonos—may occur. Sphincter spasm causes urinary retention or constipation. Dysphagia may interfere with nutrition. Characteristic painful, generalized tonic spasms with profuse sweating are precipitated by minor disturbances such as a draft, noise, or movement. Mental status is usually clear, but coma may follow repeated spasms. During generalized spasms, patients are unable to speak or cry out because of chest wall rigidity or glottal spasm. Spasms also interfere with respiration, causing cyanosis or fatal asphyxia. The immediate cause of death may not be apparent.

Respiratory failure is the most common cause of death. Laryngeal spasm and rigidity and spasms of the abdominal wall, diaphragm, and chest wall muscles cause asphyxiation. Hypoxemia can also induce cardiac arrest, and pharyngeal spasm leads to aspiration of oral secretions with subsequent pneumonia, contributing to a hypoxemic death.

Autonomic instability: Temperature is only moderately elevated unless a complicating infection, such as pneumonia, is present. Respiratory and pulse rates are increased. Reflexes are often exaggerated. Protracted tetanus may manifest as a very labile and overactive sympathetic nervous system, including periods of hypertension, tachycardia, and myocardial irritability.

Localized tetanus: In localized tetanus, there is spasticity of muscles near the entry wound but no trismus; spasticity may persist for weeks.

Cephalic tetanus is a form of localized tetanus that affects the cranial nerves. It is more common among children; in them, it may occur with chronic otitis media or may follow a head wound. Incidence is highest in Africa and India. All cranial nerves can be involved, especially the 7th. Cephalic tetanus may become generalized.

Tetanus neonatorum: Tetanus in neonates is usually generalized and frequently fatal. It often begins in an inadequately cleansed umbilical stump in children born of inadequately immunized mothers. Onset during the first 2 wk of life is characterized by rigidity, spasms, and poor feeding. Bilateral deafness may occur in surviving children.

Diagnosis

• Clinical evaluation

A history of a recent wound in a patient with muscle stiffness or spasms is a clue. Tetanus can be confused with meningoencephalitis of bacterial or viral origin, but the combination of an intact sensorium, normal CSF, and muscle spasms suggests tetanus. Trismus must be distinguished from peritonsillar or retropharyngeal abscess or another local cause. Phenothiazines can induce tetanus-like rigidity (eg, dystonic reaction, neuroleptic malignant syndrome).

C. tetani can sometimes be cultured from the wound, but culture is not sensitive.

Prognosis

Tetanus has a worldwide mortality rate of 50%, 15 to 60% in untreated adults, and 80 to 90% in neonates even if treated. Mortality is highest at the extremes of age and in drug abusers. The prognosis is poorer if the incubation period is short and symptoms progress rapidly or if treatment is delayed. The course tends to be milder when there is no demonstrable focus of infection.

Treatment

• Supportive care, particularly respiratory support

• Wound debridement

• Tetanus antitoxin

• Benzodiazepines for muscle spasms

• Metronidazole or penicillin

• Sometimes drugs for autonomic dysfunction

Therapy requires maintaining adequate ventilation. Additional interventions include early and adequate use of human immune globulin to neutralize nonfixed toxin; prevention of further toxin production; sedation; control of muscle spasm, hypertonicity, fluid balance, and intercurrent infection; and continuous nursing care.

General principles: The patient should be kept in a quiet room. Three principles should guide all therapeutic interventions: prevent further toxin release by debriding the wound and giving an antibiotic (see p. 1298); neutralize toxin outside the CNS with human tetanus immune globulin and tetanus toxoid, taking care to inject into different body sites and thus avoid neutralizing the antitoxin; and minimize the effect of toxin already in the CNS.

Wound care: Because dirt and dead tissue promote *C. tetani* growth, prompt, thorough debridement, especially of deep puncture wounds, is essential. Antibiotics are not substitutes for adequate debridement and immunization.

Antitoxin: The benefit of human-derived antitoxin depends on how much tetanospasmin is already bound to the synaptic membranes—only free toxin is neutralized. For adults, human tetanus immune globulin 3000 units IM is given once; this large volume may be split and given at separate sites. Dose can range from 1,500 to 10,000 units, depending on wound severity, although some authorities feel that 500 units are adequate. Antitoxin of animal origin is far less preferable because it does not maintain the patient's serum antitoxin level well and risk of serum sickness is considerable. If horse serum must be used, the usual dose is 50,000 units IM or IV (CAUTION: See Drug Hypersensitivity on p. 1122). If necessary, immune globulin or antitoxin can be injected directly into the wound, but this injection is not as important as good wound care.

Management of muscle spasm: Drugs are used to manage spasms.

Benzodiazepines are the standard of care to control rigidity and spasms. They block reuptake of an endogenous inhibiting neuro-transmitter, γ-aminobutyric acid (GABA), at the GABA$_A$ receptor.

Diazepam can help control seizures, counter muscle rigidity, and induce sedation. Dosage varies and requires meticulous titration and close observation. The most severe cases may require 10 to 20 mg IV q 3 h (not exceeding 5 mg/kg). Less severe cases can be controlled with 5 to 10 mg po q 2 to 4 h. Dosage varies by age:

• Infants > 30 days: 1 to 2 mg IV given slowly, repeated q 3 to 4 h as necessary

• Young children: 0.1 to 0.8 mg/kg/day up to 0.1 to 0.3 mg/kg IV q 4 to 8 h

• Children > 5 yr: 5 to 10 mg IV q 3 to 4 h

• Adults: 5 to 10 mg po q 4 to 6 h or up to 40 mg/h IV drip

Diazepam has been used most extensively, but midazolam (adults, 0.1 to 0.3 mg/kg/h IV infusion; children, 0.06 to 0.15 mg/kg/h IV infusion) is water soluble and preferred for prolonged therapy. Midazolam reduces risk of lactic acidosis due to propylene glycol solvent, which is required for diazepam and lorazepam, and reduces risk of long-acting metabolites accumulating and causing coma.

Benzodiazepines may not prevent reflex spasms, and effective respiration may require neuromuscular blockade with vecuronium 0.1 mg/kg IV or other paralytic drugs and mechanical ventilation. Pancuronium has been used but may worsen autonomic instability. Vecuronium is free of adverse cardiovascular effects but is short-acting. Longer-acting drugs (eg, pipecuronium, rocuronium) also work, but no randomized clinical comparative trials have been done.

Intrathecal baclofen (a GABA$_A$ agonist) is effective but has no clear advantage over benzodiazepines. It is given by continuous infusion; effective doses range between 20 and 2000 μg/day. A test dose of 50 μg is given first; if response is inadequate, 75 μg may be given 24 h later, and 100 μg 24 h after that. Patients who do not respond to 100 μg are not candidates for chronic infusion. Coma and respiratory depression requiring ventilatory support are potential adverse effects.

Dantrolene (loading dose 1.0 to 1.5 mg/kg IV, followed by infusion of 0.5 to 1.0 mg/kg q 4 to 6 h for ≤ 25 days) relieves muscle spasticity. Dantrolene given orally can be used in place of infusion therapy for up to 60 days. Hepatotoxicity and expense limit its use.

Management of autonomic dysfunction: Morphine may be given q 4 to 6 h to control autonomic dysfunction, especially cardiovascular; total daily dose is 20 to 180 mg. β-Blockade with long-acting drugs such as propranolol is not recommended. Sudden cardiac death is a feature of tetanus, and β-blockade can increase risk; however, esmolol, a short-acting β-blocker, has been used successfully. Atropine at high doses has been used; blockade of the parasympathetic nervous system markedly reduces excessive sweating and secretions. Lower mortality has been reported in clonidine-treated patients than in those treated with conventional therapy.

Mg sulfate at doses that maintain serum levels between 4 to 8 mEq/L (eg, 4 g bolus followed by 2 to 3 g/h) has a stabilizing effect, eliminating catecholamine stimulation. Patellar tendon reflex is used to assess overdosage. Tidal volume may be impaired, so ventilatory support must be available.

Pyridoxine (100 mg once/day) lowers mortality in neonates. Other drugs that may prove useful include Na valproate (which blocks GABA-aminotransferase, inhibiting GABA catabolism), ACE inhibitors (which inhibit angiotensin II and reduce norepinephrine release from nerve endings), dexmedetomidine (a potent α-2 adrenergic agonist), and adenosine (which reduces presynaptic norepinephrine release and antagonizes the inotropic effect of catecholamines). Corticosteroids are of unproven benefit; their use is not recommended.

Antibiotics: The role of antibiotic therapy is minor compared with wound debridement and general

support. Typical antibiotics include penicillin G 6 million units IV q 6 h, doxycycline 100 mg po bid, and metronidazole 500 mg po q 6 to 8 h.

Supportive care: In moderate or severe cases, patients should be intubated. Mechanical ventilation is essential when neuromuscular blockade is required to control muscle spasms that impair respirations.

IV hyperalimentation avoids the hazard of aspiration secondary to gastric tube feeding. Because constipation is usual, stools should be kept soft. A rectal tube may control distention. Bladder catheterization is required if urinary retention occurs.

Chest physiotherapy, frequent turning, and forced coughing are essential to prevent pneumonia. Analgesia with opioids is often needed.

Prevention

A series of 4 primary immunizations against tetanus, followed by boosters every 10 yr, with the adsorbed (for primary immunization) or fluid (for boosters) toxoid is superior to giving antitoxin at the time of injury. Tetanus toxoid comes by itself, combined with diphtheria in both adult (Td) and child strengths (DT), and combined with diphtheria and pertussis (DTP). For routine diphtheria, tetanus, and pertussis immunization and booster recommendations, see Ch. 131. Adults need to maintain immunity with regular boosters q 10 yr. Immunization in an unimmunized or inadequately immunized pregnant woman produces both active and passive immunity in the fetus and should be given at a gestational age of 5 to 6 mo with a booster at 8 mo. Passive immunity develops when maternal toxoid is given before a gestational age of 6 mo.

After injury, tetanus vaccination is given depending on wound type and vaccination history; tetanus immune globulin may also be indicated (see Table 140-1). Patients not previously vaccinated are given a 2nd and 3rd dose of toxoid at monthly intervals.

Because tetanus infection does not confer immunity, patients who have recovered from clinical tetanus should be vaccinated.

Mixed Anaerobic Infections

Anaerobes can infect normal hosts and hosts with compromised resistance or damaged tissues. Symptoms depend on site of infection. Anaerobes are often accompanied by aerobic organisms. Diagnosis is clinical combined with Gram stain and anaerobic cultures. Treatment is with antibiotics and surgical drainage and debridement.

Hundreds of species of nonsporulating anaerobes are part of the normal flora of the skin, mouth, GI tract, and vagina. If this commensal relationship is disrupted (eg, by surgery, other trauma, poor blood supply, or tissue necrosis), a few of these species can cause infections with high morbidity and mortality. After becoming established in a primary site, organisms can spread hematogenously to distant sites. Because aerobic and anaerobic bacteria are frequently present in the same infected site, appropriate procedures for isolation and culture are necessary to keep from overlooking the anaerobes. Anaerobes can be the main cause of infection in the pleural spaces and lungs; in intra-abdominal, gynecologic, CNS, upper respiratory tract, and cutaneous diseases; and in bacteremia.

Etiology

The principal anaerobic gram-positive cocci that cause disease are peptococci and peptostreptococci, which are part of the normal flora of the mouth, upper respiratory tract, and large intestine. The principal anaerobic gram-negative bacilli include *Bacteroides*

[**Table 140-1.** Tetanus Prophylaxis in Routine Wound Management]

fragilis, *Prevotella melaninogenica*, and *Fusobacterium* sp. The *B. fragilis* group is part of the normal bowel flora and includes the anaerobic pathogens most frequently isolated from intra-abdominal

infections. Organisms in the *Prevotella* group and *Fusobacterium* sp are part of the normal oral flora.

Pathophysiology

Anaerobic infections can usually be characterized as follows:

• They tend to occur as localized collections of pus or abscesses.

• The reduced O_2 tension and low oxidation-reduction potential that prevail in avascular and necrotic tissues are critical for their survival.

• When bacteremia occurs, it usually does not lead to disseminated intravascular coagulation (DIC) and purpura.

Some anaerobic bacteria possess distinct virulence factors. The virulence factors of *B. fragilis* probably account for its frequent isolation from clinical specimens despite its relative rarity in normal flora. This organism has a polysaccharide capsule that apparently stimulates abscess formation. An experimental model of intra-abdominal sepsis has shown that *B. fragilis* alone can cause abscesses, whereas other *Bacteroides* sp require the synergistic effect of another organism. Another virulence factor, a potent endotoxin, is implicated in septic shock associated with severe *Fusobacterium* pharyngitis.

Morbidity and mortality rates for anaerobic and mixed bacterial sepsis are as high as those for sepsis caused by a single aerobic organism. Anaerobic infections are often complicated by deep-seated tissue necrosis. The overall mortality rate for severe intra-abdominal sepsis and mixed anaerobic pneumonias tends to be high. *B. fragilis* bacteremia has a high mortality rate, especially in the elderly and in patients with cancer.

Symptoms and Signs

Patients usually have fever, rigors, and critical illness; shock may develop. DIC may occur in *Fusobacterium* sepsis.

For specific infections (and symptoms) caused by mixed anaerobic organisms, see elsewhere in THE MANUAL and
Table 140-2. Anaerobes are rare in UTI, septic arthritis, and infective endocarditis.

Diagnosis

• Clinical suspicion

• Gram stain and culture

[**Table 140-2.** Disorders Often Caused by Mixed* Anaerobic Organisms]

Clinical clues to the presence of anaerobic organisms include

• Infection adjacent to mucosal surfaces that bear anaerobic flora

• Ischemia, tumor, penetrating trauma, foreign body, or perforated viscus

• Spreading gangrene involving skin, subcutaneous tissue, fascia, and muscle

• Feculent odor in pus or infected tissues

• Abscess formation

• Gas in tissues

• Septic thrombophlebitis

• Failure to respond to antibiotics that do not have significant anaerobic activity

Anaerobic infection should be suspected when any wound smells foul or when a Gram stain of pus from an infected site shows mixed pleomorphic bacteria. Only specimens from normally sterile sites should be cultured because commensal contaminants may easily be mistaken for pathogens.

Gram stains and aerobic cultures should be obtained for all specimens. Gram stain, particularly in *Bacteroides* infection, and cultures for all anaerobes may be falsely negative. Antibiotic sensitivity testing of anaerobes is exacting, and data may not be available for ≥ 1 wk after initial culture. However, if the species is known, sensitivity patterns can usually be predicted. Therefore, many laboratories do not routinely test anaerobic organisms for sensitivity.

Treatment

• Drainage and debridement

• Antibiotic choice varying by site of infection

In established infection, pus is drained, and devitalized tissue, foreign bodies, and necrotic tissue are removed. Organ perforations must be treated by closure or drainage. Whenever possible, blood supply should be reestablished. Septic thrombophlebitis may require vein ligation as well as antibiotics.

Because anaerobic culture results may not be available for 3 to 5 days, antibiotics are started. Antibiotics sometimes work even when some of the bacterial species in a mixed infection are resistant to the antibiotic, especially if surgical debridement and drainage are adequate.

Oropharyngeal anaerobic infections may not respond to penicillin and thus require a drug effective against penicillin-resistant anaerobes (see below). Oropharyngeal infections and lung abscesses should be treated with clindamycin or a β-lactam/β-lactamase combination such as amoxicillin/clavulanate. In patients allergic to penicillin, clindamycin or metronidazole (plus a drug active against aerobes) is useful.

GI or female pelvic anaerobic infections are likely to contain obligate anaerobic gram-negative bacilli such as *B. fragilis* plus facultative gram-negative bacilli such as *Escherichia* coli; antibiotic regimens must be active against both. Resistance of *B. fragilis* and other obligate anaerobic gram-negative bacilli to penicillins and 3rd- and 4th-generation cephalosporins occurs. However, the following drugs have excellent in vitro activity against *B. fragilis* and are effective: metronidazole, carbapenems (eg, imipenem/cilastatin, meropenem, ertapenem), β-lactam/β-lactamase combinations (eg, piperacillin/tazobactam, ampicillin/sulbactam, amoxicillin/clavulanate, ticarcillin/clavulanate), tigecycline, and moxifloxacin. No single regimen appears to be superior. Drugs that are somewhat less predictably active in vitro against *B. fragilis* but are usually effective include clindamycin, cefoxitin, and cefotetan. All except clindamycin and metro-nidazole can be used as monotherapy because these drugs also have good activity against facultative anaerobic gram-negative bacilli.

Metronidazole is active against clindamycin-resistant *B. fragilis*, has unique anaerobic bactericidal activity, and usually avoids the pseudomembranous colitis sometimes associated with clindamycin. Concerns about metronidazole's potential mutagenicity have not been of clinical consequence.

Because many regimens are available to treat GI or female pelvic anaerobic infections, use of a potentially nephrotoxic aminoglycoside (to cover enteric gram-negative bacilli) plus an antibiotic active against *B. fragilis* is no longer warranted.

Prevention

• Metronidazole plus gentamicin or ciprofloxacin

Before elective colorectal surgery, patients should have bowel preparation consisting of

• Cathartics

• Enemas

• Antibiotics

Most surgeons give both oral and parenteral antibiotics. For emergency colorectal surgery, parenteral antibiotics are used alone. Examples of oral regimens are neomycin plus erythromycin or neomycin plus metronidazole; these drugs are given no more than 18 to 24 h before the procedure. Examples of parenteral preoperative regimens are cefotetan, cefoxitin, or cefazolin plus metronidazole. Preoperative parenteral antibiotics control bacteremia, reduce secondary or metastatic suppurative complications, and prevent local spread of infection around the surgical site.

For patients with confirmed allergy or adverse reaction to β-lactams, one of the following regimens is recommended: clindamycin plus gentamicin, aztreonam, or ciprofloxacin; or metronidazole plus gentamicin or ciprofloxacin.

Chapter 141. Mycobacteria

Introduction

Mycobacteria are small, slow-growing, aerobic bacilli distinguished by a complex, lipid-rich cell envelope responsible for their characterization as acid-fast (ie, resistant to decolorization by acid after staining with carbolfuchsin) and their imperviousness to Gram stain. The most common mycobacterial infection is tuberculosis; others include leprosy and various diseases caused by *Mycobacterium avium* complex.

Tuberculosis

(See also Perinatal Tuberculosis on p. 2838.)

Tuberculosis (TB) is a chronic, progressive infection with a period of latency following initial infection. It occurs most commonly in the lungs. Pulmonary symptoms include productive cough, chest pain, and dyspnea. Diagnosis is most often by sputum culture and smear. Treatment is with multiple antimicrobial drugs.

TB is a leading infectious cause of morbidity and mortality in adults worldwide, killing about 1.5 million people every year. HIV/AIDS is an increasingly prominent factor predisposing to TB infection and mortality in parts of the world where both infections are prevalent.

Etiology

TB properly refers only to disease caused by *Mycobacterium tuberculosis*. Similar disease occasionally results from the closely related mycobacteria, *M. bovis, M. africanum*, and *M. microti*.

TB results almost exclusively from inhalation of airborne particles (droplet nuclei) containing *M. tuberculosis*. They disperse primarily through coughing, singing, and other forced respiratory maneuvers by people who have active pulmonary TB and whose sputum contains a significant number of organisms (typically enough to render the smear positive). People with pulmonary cavitary lesions are especially infectious. Droplet nuclei containing tubercle bacilli may remain suspended in room air currents for several hours, increasing the chance of spread. However, once these droplets land on a surface, it is difficult to resuspend the organisms (eg, by sweeping the floor, shaking out bed linens) as respirable particles. Although such actions can resuspend dust particles containing tubercle bacilli, these particles are far too large to reach the alveolar surfaces necessary to initiate infection. Fomites (eg, contaminated surfaces, food, and personal respirators) do not appear to facilitate spread.

Although there is wide variability, patients with pulmonary TB infect about 7 close contacts, on average, but most of those infected do not develop active disease. Transmission is enhanced by frequent or prolonged exposure to a patient who is dispersing large numbers of tubercle bacilli in overcrowded, enclosed, poorly ventilated spaces; thus, people living in poverty or in institutions are at particular risk. Health care practitioners who have close contact with active cases have increased risk. However, once effective treatment begins, cough rapidly decreases, organisms are inactivated, and within weeks, TB is no longer contagious.

Much less commonly, spread results from aerosolization of organisms after irrigation of infected wounds, in mycobacteriology laboratories, or in autopsy rooms. TB of the tonsils, lymph nodes, abdominal organs, bones, and joints was once commonly caused by ingestion of milk or milk products (eg, cheese) contaminated with *M. bovis*, but this transmission route has been largely eradicated in developed countries by slaughter of cows that test positive on a tuberculin skin test and by pasteurization of milk. Tuberculosis due to *M. bovis* still occurs in developing countries and in immigrants from developing countries where bovine tuberculosis is endemic (eg, some Latin American countries).

Risk factors: HIV infection is the greatest single medical risk factor because cell-mediated immunity, which is impaired by HIV, is essential for defense against TB; other immunosuppressive illnesses (eg, diabetes) or therapies (eg, tumor necrosis factor [TNF] inhibitors, corticosteroids) increase risk but less

than HIV.

Age has traditionally been considered an independent risk factor because the elderly have more years of potential exposure and are more likely to have impaired immunity. However, in the US, the difference in the age-specific case rate is no longer as large, probably because the incidence of infectious cases (and hence lifetime risk of significant exposure) has declined.

Epidemiology

About one third of the world's population is infected. Of these, perhaps only 15 million have active disease at any given time. In 2006, an estimated 9.2 million new TB cases occurred worldwide (139/100,000). Of these, Africa and Southeast Asia each accounted for about 3 million cases, and the Western Pacific region for about 2 million. Case rates vary very widely by country, age, race, sex, and socioeconomic status. India and China reported the largest numbers of new cases, but South Africa has the largest case rate: 940/100,000.

In the US, the case rate has declined 10-fold since 1953. In 2007, 13,299 cases were reported to the CDC for a case rate of 4.4/100,000 (ranging from 0.4 in Wyoming to 10.2 in Washington DC). Over half of these cases occurred in patients born outside the US in high-prevalence areas. The TB rate among foreign-born people (20.7/100,000) was nearly 10 times the rate among US-born people (2.1/100,000). Blacks accounted for 45% of cases among the US-born. In the southeastern US and inner cities throughout the US, poor US-born blacks, the homeless, people in jails and prisons, and other disenfranchised minorities contribute disproportionately to the case rate. In such high-risk populations, case rates can approach those in high-burden parts of the world.

A resurgence of TB occurred in parts of the US and other developed countries between 1985 and 1992; it was associated with several factors, including HIV coinfection, homelessness, a deteriorated public health infrastructure, and the appearance of multidrug-resistant TB (MDR-TB). Although substantially controlled in the US by public health and institutional infection control measures, the problem of MDR-TB, including extensively drug-resistant TB (XDR-TB), appears to be growing around the world, fueled by poor treatment supervision, weak retreatment regimens, inadequate drug supplies, HIV coinfection, institutional transmission, and inadequate diagnostic laboratory facilities. Control efforts, including prolonged (eg, > 18 mo) use of 2nd-line antibiotics, treatment of adverse drug reactions, community-based supervision, social and emotional support, and improved institutional transmission control are raising hopes for better global control of MDR-TB. Treatment of XDR-TB has less favorable outcomes, and the mortality rate is extremely high in patients coinfected with HIV despite concomitant antiretroviral therapy.

Pathophysiology

Tubercle bacilli initially cause a primary infection, which only rarely causes acute illness. Most (about 95%) primary infections are asymptomatic and followed by a latent (dormant) phase. However, a variable percentage of latent infections subsequently reactivate with symptoms and signs of disease. Infection is usually not transmissible in the primary stage and is never contagious in the latent stage.

Primary infection: Infection requires inhalation of particles small enough to traverse the upper respiratory defenses and deposit deep in the lung, usually in the subpleural airspaces of the lower lung. Large droplets tend to lodge in the more proximal airways and typically do not result in infection. Infection usually begins from a single initial focus.

To initiate infection, tubercle bacilli must be ingested by alveolar macrophages. Tubercle bacilli that are not killed by the macrophages actually replicate inside them, ultimately killing the host macrophage (with the help of CD8 lymphocytes); inflammatory cells are attracted to the area, causing a focal pneumonitis that evolves into the characteristic tubercles seen histologically. In the early weeks of infection, some infected macrophages migrate to regional lymph nodes (eg, hilar, mediastinal), where they access the bloodstream. Organisms may then spread hematogenously to any part of the body, particularly the apical-posterior portion of the lungs, epiphyses of the long bones, kidneys, vertebral bodies, and meninges.

In 95% of cases, after about 3 wk of uninhibited growth, the immune system suppresses bacillary replication before symptoms or signs develop. Foci of infection in the lung or other sites resolve into epithelioid cell granulomas, which may have caseous and necrotic centers. Tubercle bacilli can survive in this material for years; the balance between the host's resistance and microbial virulence determines whether the infection ultimately resolves without treatment, remains dormant, or becomes active. Infectious foci may leave fibronodular scars in the apices of one or both lungs (Simon foci), calcified scars from the primary infection (Ghon foci), or calcified hilar lymph nodes. The tuberculin skin test (see p. 1305) and the newer interferon-γ release assay become positive.

Less often, the primary focus immediately progresses, causing acute illness with pneumonia (sometimes cavitary), pleural effusion, and marked mediastinal or hilar lymph node enlargement (which, in children, may compress bronchi). Small pleural effusions are predominantly lymphocytic, typically contain few organisms, and clear within a few weeks. This sequence may be more common among young children and recently infected or reinfected immunosuppressed patients. Extrapulmonary TB at any site can sometimes manifest without evidence of lung involvement. TB lymphadenopathy is the most common extrapulmonary presentation; however, meningitis is the most feared because of its high mortality in the very young and very old.

Active disease: In about 10% of immunocompetent patients, latent infection develops into active disease, although the percentage varies significantly by age and other risk factors. In 50 to 80% of those who develop active disease, TB reactivates within the first 2 yr, but it can occur decades later. Any organ initially seeded may become a site of reactivation, but reactivation occurs most often in the lung apices, presumably because of favorable local conditions such as high O_2 tension. Ghon foci and affected hilar lymph nodes are much less likely to be sites of reactivation.

Conditions that facilitate activation include impaired immunity (particularly HIV infection), certain immunosuppressants (eg, corticosteroids, infliximab, other TNF inhibitors), gastrectomy, jejunoileal bypass surgery, silicosis, renal insufficiency, stress, diabetes, head or neck cancer, significant weight loss, adolescence, and advanced age (particularly > 70 yr).

TB damages tissues through delayed-type hypersensitivity (DTH—see p. 1109), typically producing granulomatous necrosis with a caseous histologic appearance. Lung lesions are characteristically but not invariably cavitary, especially in immunosuppressed patients with impaired DTH. Pleural effusion is less common than in progressive primary TB but may result from direct extension or hematogenous spread. Rupture of a large tuberculous lesion into the pleural space may cause empyema with or without bronchopleural fistula and sometimes causes pneumothorax. In the prechemotherapy era, TB empyema sometimes complicated medically induced pneumothorax therapy and was usually rapidly fatal, as was sudden massive hemoptysis due to erosion of a pulmonary artery by an enlarging cavity.

The course varies greatly, depending on the virulence of the organism and the state of host defenses. The course may be rapid among blacks, American Indians, and other populations who have not had as many centuries of selective pressure to develop innate or natural immunity as descendents of the European and American TB epidemics have had. The course is often more indolent in the latter populations.

Acute respiratory distress syndrome (ARDS), which appears to be due to hypersensitivity to TB antigens, develops rarely after diffuse hematogenous spread or rupture of a large cavity with spillage into the lungs.

Symptoms and Signs

In active pulmonary TB, even moderate or severe disease, patients may have no symptoms, except "not feeling well," anorexia, fatigue, and weight loss, which develop gradually over several weeks, or they may have more specific symptoms. Cough is most common. At first, it may be minimally productive of yellow or green sputum, usually on rising, but cough may become more productive as the disease progresses. Hemoptysis occurs only with cavitary TB (sometimes due to fungal growth in a cavity). Low-grade fever is common but not invariable. Drenching night sweats are a classic symptom but are neither common in nor specific for TB. Dyspnea may result from lung parenchymal damage, spontaneous pneumothorax, or pleural TB with effusion.

With HIV coinfection, the clinical presentation is often atypical because DTH is impaired; patients are more likely to have symptoms of extrapulmonary or disseminated disease.

Diagnosis

• Chest x-ray

• Tuberculin skin test

• Acid-fast stain and culture

• When available, DNA-based testing

Pulmonary TB is often suspected based on chest x-rays taken while evaluating respiratory symptoms (cough > 3 wk, hemoptysis, chest pain, dyspnea), an unexplained illness, FUO, or a positive tuberculin skin test (see p.).

Initial tests are chest x-ray, sputum examination, and tuberculin skin testing. If the chest x-ray is highly characteristic (upper lobe lung cavitation) in patients with TB risk factors, sputum examination is still required, but skin testing is often not done.

Chest x-ray: In adults, a multinodular infiltrate above or behind the clavicle (the most characteristic location, most visible in an apical-lordotic view or with CT) suggests reactivation of TB. Middle and lower lung infiltrates are nonspecific but should prompt suspicion of primary TB in patients (usually young) whose symptoms or exposure history suggests recent infection, particularly if there is pleural effusion. Calcified hilar nodes may be present; they may result from primary TB infection but also may result from histoplasmosis in areas where histoplasmosis is endemic (eg, the Ohio River Valley).

Sputum examination: Sputum is tested for the presence of acid-fast bacilli (AFB). Tubercle bacilli are nominally gram-positive but take up Gram stain inconsistently; samples are best prepared with Ziehl-Neelsen or Kinyoun stains for conventional light microscopy or fluorochrome stains for fluorescent microscopy.

If patients cannot produce sputum spontaneously, aerosolized hypertonic saline can be used to induce it. If induction is unsuccessful, bronchial washings, which are particularly sensitive, can be obtained by fiberoptic bronchoscopy. Because induction of sputum and bronchoscopy entail some risk of infection for medical staff, these procedures should be done as a last resort in selected cases when MDR-TB is not likely. Appropriate precautions (eg, negative-pressure room, N-95 or other fitted respirators) should be used.

In addition to acid-fast staining, sputum can be tested using nucleic acid amplification techniques (NAAT) for TB; this test can shorten the time needed to diagnose TB from 1 to 2 wk to 1 to 2 days. However, in low-prevalence situations, this test is usually done only on smear-positive specimens. It is approved for smear-negative specimens and is indicated when suspicion is high and a rapid diagnosis is essential for medical or public health reasons.

If NAAT and AFB smear results are positive, patients are presumed to have TB and treatment can be started. If the NAAT result is positive and the AFB smear result is negative, an additional specimen is tested using NAAT; patients can be presumed to have TB if ≥ 2 specimens are NAAT-positive. If NAAT and AFB smear results are negative, clinical judgment is used to determine whether to begin anti-TB treatment while awaiting results of culture.

The finding of acid-fast bacilli in a sputum smear is strong presumptive evidence of TB, but definitive diagnosis requires a positive sputum culture or NAAT. Culture is also required for isolating bacteria for drug-susceptibility testing and genotyping.

Drug susceptibility tests (DSTs) should be done on initial isolates from all patients to identify an

effective anti-TB regimen. These tests should be repeated if patients continue to produce culture-positive sputum after 3 mo of treatment or if cultures become positive after a period of negative cultures. Results of DSTs may take up to 8 wk if conventional bacteriologic methods are used. However, several new molecular DSTs can detect drug resistance in a sputum sample within hours.

Tests of other specimens: Transbronchial biopsies can be done on infiltrative lesions, and samples are submitted for culture, histologic evaluation, and molecular testing. Gastric washings, which are culture-positive in a minority of samples, are no longer commonly used except in small children, who usually cannot produce a good sputum specimen. Ideally, biopsied samples of other tissue should be cultured fresh, but NAAT can be used for fixed tissues (eg, for biopsied lymph node if histologic examination unexpectedly detects granulomatous changes). The latter use of NAAT has not been approved but can be extremely useful, although positive and negative predictive values have not been established.

Skin testing: Multiple-puncture devices (tine test) are no longer recommended. The tuberculin skin test (TST; Mantoux or PPD—purified protein derivative) is usually done, although it is a test of infection, latent or active, and is not diagnostic of active disease. The standard dose in the US of 5 tuberculin units (TU) of PPD in 0.1 mL of solution is injected on the volar forearm. It is critical to give the injection intradermally, not subcutaneously. A well-demarcated bleb or wheal should result immediately. The diameter of induration (not erythema) transverse to the long axis of the arm is measured 48 to 72 h after injection. Recommended cutoff points for a positive reaction depend on the clinical setting:

- **5 mm:** Patients at high risk of developing active TB if infected, such as those who have chest x-ray evidence of past TB, who are immunosuppressed because of HIV infection or drugs (eg, TNF-α inhibitors, corticosteroid use equivalent to prednisone 15 mg/day for > 1 mo), or who are close contacts of patients with infectious TB

- **10 mm:** Patients with some risk factors, such as injection drug users, recent immigrants from high-prevalence areas, residents of high-risk settings (eg, prisons, homeless shelters), patients aged > 70 yr, those with certain disorders (eg, silicosis, renal insufficiency, diabetes, head or neck cancer), and those who have had gastrectomy or jejunoileal bypass surgery

- **15 mm:** Patients with no risk factors (who typically should not be tested)

Results can be falsely negative, most often in patients who are febrile, elderly, HIV-infected (especially if CD4+ count is < 200 cells/μL), or very ill, many of whom show no reaction to any skin test (anergy). Anergy probably occurs because inhibiting antibodies are present or because so many T cells have been mobilized to the disease site that too few remain to produce a significant skin reaction.

Other tests: New blood tests based on the release of interferon-γ by lymphocytes exposed in vitro to TB-specific antigens are now available and are likely to soon replace the TST for routine testing for TB infection. Although results of interferon-γ release assays (IGRAs) are not always concordant with TST, these tests appear to be as sensitive as and more specific than TST in contact investigations. Importantly, they are often negative in patients with remote TB infection. Long-term studies are being done to see whether TST-positive, IGRA-negative patients (particularly those with immunosuppression) are at low risk of reactivation.

Prognosis

In immunocompetent patients with drug-susceptible pulmonary TB, even severe disease and large cavities usually resolve if appropriate therapy is instituted and completed. Still, TB causes or contributes to death in about 10% of cases, often in patients who are debilitated for other reasons. Disseminated TB and TB meningitis may be fatal in up to 25% of cases despite optimal treatment.

TB is much more aggressive in immunocompromised patients and, if not appropriately and aggressively treated, may be fatal in as little as 2 mo from its initial symptom, especially with MDR-TB, in which mortality can approach 90%. With effective antiretroviral therapy (and appropriate anti-TB treatment), the prognosis for immunocompromised patients, even with MDR-TB, may approach that of immunocompetent patients. However, poorer outcomes should be expected for patients with XDR-TB because there are so

few effective drugs.

Treatment

Most patients with uncomplicated TB and all patients with complicating illnesses (eg, AIDS, hepatitis, diabetes), adverse drug reactions, or drug resistance should be referred to a TB specialist. However, most TB can be fully treated at home with instructions on how to avoid spreading disease; these measures include

• Staying at home

• Avoiding visitors (previously exposed family members may stay)

• Covering coughs with a tissue or hand

Surgical face masks for TB patients are stigmatizing and are generally not recommended for cooperative patients. For drug-susceptible TB that is being treated effectively, precautions must be continued for at least 2 wk in or outside the hospital. For patients with MDR-TB and XDR-TB, response to treatment may be slower, and the consequences of transmission greater; thus, precautions are continued longer, until there is clear evidence of treatment response.

Hospitalization: The main indications for hospitalization are

• Serious concomitant illness

• Need for diagnostic procedures

• Social issues (eg, homelessness)

• Need for respiratory isolation, as for people living in congregate settings where previously unexposed people would be regularly encountered

Initially, all hospitalized patients should be in respiratory isolation, ideally in a negative-pressure room with 6 to 12 air changes/h. Anyone entering the room should wear a respirator (not a surgical mask) that has been appropriately fitted and that meets National Institute for Occupational Safety and Health certification (N-95 or greater). Because risk of exposing other hospitalized patients is high, release from respiratory isolation usually requires 3 negative sputum smears over 2 days, including at least one early-morning negative specimen.

Public health considerations: To improve treatment adherence, ensure cure, and limit transmission and the development of drug-resistant strains, public health programs closely monitor treatment, even if patients are being treated by a private physician. In most states, TB care (including skin testing, chest x-rays, and drugs) is available free through public health clinics to reduce barriers to treatment.

Increasingly, optimal patient case management includes supervision by public health personnel of the ingestion of every dose of drug, a strategy known as directly observed therapy (DOT). DOT increases the likelihood that the full treatment course will be completed from 61% to 86% (91% with enhanced DOT, in which incentives and enablers such as transportation vouchers, child care, outreach workers, and meals are provided). DOT is particularly important

• For children and adolescents

• For patients with HIV infection, psychiatric illness, or substance abuse

• After treatment failure, relapse, or development of drug resistance

In some programs, selective self-administered treatment (SAT) is an option for patients who are committed to treatment; ideally, fixed-dose combination drug preparations are used to avoid the possibility of

monotherapy, which can lead to drug resistance. Mechanical drug monitors have been advocated to improve adherence with SAT.

Public health departments usually visit homes to evaluate potential barriers to treatment (eg, extreme poverty, unstable housing, child care problems, alcoholism, mental illness) and to check for other active cases and close contacts. Close contacts are people who share the same breathing space for prolonged periods, typically household residents, but often include people at work, school, and places of recreation. The precise duration and degree of contact that constitutes risk vary because TB patients vary greatly in infectiousness. For patients who are highly infectious as evidenced by multiple family members with disease or positive skin tests, even relatively casual contacts (eg, passengers on the bus they ride) should be referred for skin testing and evaluation for latent infection (see p.); patients who do not infect any household contacts are less likely to infect casual contacts.

First-line drugs: The first-line drugs isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) are used together in initial treatment (for regimens and doses, see p. and Table 141-1).

INH is given orally once/day, has good tissue penetration (including CSF), and is

[**Table 141-1.** Dosing of First-Line Anti-TB Drugs*]

highly bactericidal. It remains the single most useful and least expensive drug for TB treatment. However, inconsistent drug levels and decades of uncontrolled use (often as monotherapy) in many countries (especially in East Asia) have greatly increased the percentage of resistant strains. In the US, about 10% of isolates are INH-resistant. INH is safe during pregnancy.

Adverse reactions include rash, fever, and, rarely, anemia and agranulocytosis. INH causes harmless, transient aminotransferase elevations in up to 20% of patients and symptomatic (usually reversible) hepatitis in about 1/1000 (more often in patients > 35 yr, alcoholics, postpartum women, and patients with chronic liver disease). Monthly liver function testing is not recommended unless patients have risk factors for liver disease. Patients with unexplained fatigue, anorexia, nausea, vomiting, or jaundice may have hepatic toxicity; treatment is suspended and liver function tests are obtained. Those with symptoms and any significant aminotransferase elevation (or asymptomatic elevation > 5 times normal) by definition have hepatic toxicity, and INH is stopped. After recovery from mild aminotransferase elevations and symptoms, patients can be safely challenged with a half-dose for 2 to 3 days. If this dose is tolerated (typically in about half of patients), the full dose may be restarted with close monitoring for symptoms and liver function deterioration. If patients are receiving INH, RIF, and PZA, all drugs must be stopped, and the challenge done with each drug separately. INH or PZA, rather than RIF, is the more likely cause of hepatotoxicity. Peripheral neuropathy can result from INH-induced pyridoxine (vitamin B_6) deficiency, most likely in pregnant or breastfeeding women, undernourished patients, patients with diabetes mellitus or HIV infection, alcoholics, patients with cancer or uremia, and the elderly. A daily dose of pyridoxine 25 to 50 mg can prevent this complication, although pyridoxine is usually not needed in children and healthy young adults. INH delays hepatic metabolism of phenytoin, requiring dose reduction. INH can also cause a violent reaction to disulfiram, a drug occasionally used for alcoholism.

RIF, given orally, is bactericidal, is well absorbed, penetrates well into cells and CSF, and acts rapidly. It also eliminates dormant organisms in macrophages or caseous lesions that can cause late relapse. Thus, RIF should be used throughout the course of therapy. Adverse effects include cholestatic jaundice (rare), fever, thrombocytopenia, and renal failure. RIF adds only slightly to the hepatotoxicity of INH. RIF has many significant drug interactions. It accelerates metabolism of anticoagulants, oral contraceptives, corticosteroids, digitoxin, oral antihyperglycemic drugs, methadone, and many other drugs. The interactions of rifamycins and many antiretroviral drugs is particularly complex; combined use requires specialized expertise. RIF is safe during pregnancy.

The following newer rifamycins are available for special situations:

• **Rifabutin** is used for patients taking drugs (particularly antiretroviral drugs) that have unacceptable interactions with RIF. Its action is similar to RIF, but when used with clarithromycin or fluconazole, it has

been associated with uveitis.

- **Rifapentine** is used in one dose/wk regimens (see Table 141-1) but is not used in children or patients with HIV (because of unacceptable treatment failure rates) or extrapulmonary TB.

PZA is an oral bactericidal drug. When used during the intensive initial 2 mo of treatment, it shortens therapy to 6 mo and prevents development of resistance to RIF.

Its major adverse effects are GI upset and hepatitis. It often causes hyperuricemia, which is generally mild and only rarely induces gout. It is contraindicated in pregnancy. PZA plus rifampin is no longer recommended as a 2-mo regimen for latent TB because excessive hepatotoxicity can occur.

EMB is given orally and is the best tolerated of the first-line drugs. Its main toxicity is optic neuritis, which is more common at higher doses (eg, 25 mg/kg) and in patients with impaired renal function. Patients present initially with an inability to distinguish blue from green, followed by impairment of visual acuity. Because both symptoms are reversible if detected early, patients should have a baseline test of visual acuity and color vision and should be questioned monthly regarding their vision. Caution is warranted if communication is limited by language and cultural barriers. For similar reasons, EMB is usually avoided in young children who cannot read eye charts but can be used if needed because of drug resistance or drug intolerance. Another drug is substituted for EMB if optic neuritis occurs. EMB can be used safely during pregnancy. Resistance to EMB is less common than that to the other first-line drugs.

Second-line drugs: Other antibiotics are active against TB and are used primarily when patients have MDR-TB or do not tolerate one of the first-line drugs. The 2 most important classes are aminoglycosides (and the closely related polypeptide drug, capreomycin) and fluoroquinolones.

Streptomycin, the most commonly used aminoglycoside, is very effective and bactericidal. Resistance is still relatively uncommon in the US but is more common globally. CSF penetration is poor, and intrathecal administration should not be used if other effective drugs are available.

Dose-related adverse effects include renal tubular damage, vestibular damage, and ototoxicity. The dose is about 15 mg/kg IM (maximum: usually 1 g for adults, reduced to 0.75 g [10 mg/kg] for those ≥ 60 yr). To limit dose-related adverse effects, clinicians give one dose only 5 days/wk for > 2 mo. Then it may be given twice/wk for another 2 mo if necessary. In patients with renal insufficiency, dosing frequency should be reduced (eg, 12 to 15 mg/kg/dose 2 or 3 times/wk). Patients should be monitored with appropriate testing of balance, hearing, and serum creatinine levels. Adverse effects include rash, fever, agranulocytosis, and serum sickness. Flushing and tingling around the mouth commonly accompany injection but subside quickly. Streptomycin is contraindicated during pregnancy because it may damage the 8th cranial nerve in the fetus.

Kanamycin and **amikacin** may remain effective even if streptomycin resistance has developed. Their renal and neural toxicities are similar to those of streptomycin.

Capreomycin, a related nonaminoglycoside parenteral bactericidal drug, has dosage, effectiveness, and adverse effects similar to those of aminoglycosides. It is an important drug for MDR-TB because isolates resistant to streptomycin are often susceptible to capreomycin, and it is somewhat better tolerated than aminoglycosides when prolonged administration is required.

Some **fluoroquinolones** (levofloxacin, moxifloxacin) are the most active and safest TB drugs after INH and RIF, but they are not first-line drugs for TB susceptible to INH and RIF. Moxifloxacin appears to be as active as INH when used with RIF.

Other 2nd-line drugs include ethionamide, cycloserine, and para-aminosalicylic acid (PAS). These drugs are less effective and more toxic than the first-line drugs but are essential in treatment of MDR-TB.

Drug resistance: Treatment with any single antibiotic always results in survival of a very few (about 1 in a million) organisms that have acquired spontaneous resistance mutations. Incomplete or erratic therapy selects for these resistant organisms, making treatment adherence particularly important in prevention of

resistance. Multiple drugs are used concurrently for TB so that organisms resistant to one drug are killed by the others; simultaneous spontaneous mutations to multiple drugs are unlikely. However, once a strain resistant to a single drug has developed and proliferated, it may acquire resistance to additional drugs through the same process; thus, MDRTB can occur by stepwise acquired resistance to INH, RIF, and often other drugs. Some resistant strains appear to be less fit (ie, less transmissible and virulent); others have acquired compensatory mutations that restore fitness, allowing disease progression and transmission to occur.

Once a drug-resistant strain develops in a patient, it can spread from person to person (primary drug resistance). Uninhibited transmission of drug-resistant strains in congregate settings, such as hospitals, clinics, prisons, shelters, and refugee camps, is a major barrier to global control.

Several new anti-TB drugs that may be active against resistant strains are in preclinical or clinical development but will not be available for several more years. Furthermore, unless treatment programs are strengthened (eg, by full supervision of each dose), stepwise resistance to new drugs is likely.

MDR-TB is TB resistant in vitro to both isoniazid and rifampin, with or without resistance to other drugs. Numerous outbreaks of MDR-TB have been reported, and the global burden is rising. The Stop TB Partnership estimates that 780,000 new cases of MDR-TB will occur between 2006 and 2015. In parts of the world where resistance testing is inadequate or unavailable, many patients who do not respond to first-line therapy probably have MDR-TB that is undiagnosed. MDR-TB has major negative implications for TB control; alternative treatments require a longer treatment course with less effective, more toxic, and more expensive 2nd-line drugs.

XDR-TB is MDR-TB that is also resistant to fluoroquinolones and injectable drugs (eg, streptomycin, amikacin, kanamycin, capreomycin). TB strains that are resistant to other drug combinations but that do not meet the definitions of MDR or XDR are termed polyresistant. Because the fluoroquinolones and injectables are important for treatment of MDR-TB, XDR-TB has dire therapeutic implications. Although some patients can be cured, mortality is higher and depends on the number of effective drugs remaining and the extent of lung destruction. Surgery to remove localized areas of lung destruction plays an important role in the treatment of advanced cases of MDR-TB or XDR-TB but is not widely available in high-burden regions.

Treatment regimens: Treatment of all patients with new, previously untreated TB should consist of a

• 2-mo initial, intensive phase

• 4- or 7-mo continuation phase

Initial intensive-phase therapy is with 4 antibiotics: INH, RIF, PZA, and EMB (see Table 141-1 for dosing). These drugs can be given daily throughout this phase or daily for 2 wk, followed by doses 2 or 3 times/wk for 6 wk. Intermittent administration (usually with higher doses) is usually satisfactory because of the slow growth of tubercle bacilli and the residual postantibiotic effect on growth (after antibiotic inhibition, bacterial growth is often delayed well after antibiotics are below the minimal inhibitory concentration). However, daily therapy is recommended for patients with MDR-TB or HIV coinfection. Regimens involving less than daily dosing must be carried out as DOT because each dose becomes more important.

After 2 mo of intensive 4-drug treatment, PZA and usually EMB are stopped, depending on the drug susceptibility pattern of the original isolate.

Continuation-phase treatment depends on results of drug susceptibility testing of initial isolates (where available), the presence or absence of a cavitary lesion on the initial chest x-ray, and results of cultures taken at 2 mo. If positive, 2-mo cultures indicate the need for a longer course of treatment. If both culture and smear are negative, regardless of the chest x-ray, or if the culture or smear is positive but x-ray showed no cavitation, INH and RIF are continued for 4 more mo (6 mo total). If the x-ray showed cavitation and the culture or smear is positive, INH and RIF are continued for 7 more mo (9 mo total). In either regimen, EMB is stopped if the initial culture shows no resistance to any drug. Continuation-phase

drugs can be given daily or, if patients are not HIV-positive, 2 or 3 times/wk. Patients who have negative culture and smears at 2 mo and no cavitation on chest x-ray and who are HIV-negative may receive once/wk INH plus rifapentine.

For both initial and continuation phases, the total number of doses (calculated by doses/wk times number of weeks) should be given; thus if any doses are missed, treatment is extended and not stopped at the end of the time period.

Management of drug-resistant TB varies with the pattern of drug resistance. Generally, MDR-TB requires prolonged (eg, 18 to 24 mo) treatment with the remaining active first-line drugs (including PZA, if the strain is susceptible) with addition of an injectable, a fluoroquinolone, and other 2nd-line drugs as needed to build a 4- or 5-drug regimen that the infecting strain is known or likely to be susceptible to (ie, based on testing, a known source-case, prior treatment, or drug susceptibility patterns in the community). Managing the adverse effects of these long, complex regimens is challenging. MDR-TB should always be treated by a TB specialist experienced with these cases. Fully supervised treatment is essential to avoid additional drug resistance through nonadherance.

Other treatments: Surgical resection of a persistent TB cavity is occasionally necessary. The main indication for resection is persistent, culture-positive MDR-TB or XDR-TB in patients with a destroyed lung region into which antibiotics cannot penetrate. Other indications include uncontrollable hemoptysis and bronchial stenosis.

Corticosteroids are sometimes used to treat TB when inflammation is a major cause of morbidity and are indicated for patients with acute respiratory distress syndrome or closed-space infections, such as meningitis and pericarditis. Dexamethasone 12 mg po or IV q 6 h is given to adults and children > 25 kg; children < 25 kg are given 8 mg. Treatment is continued for 2 to 3 wk. Corticosteroids that are needed for other indications pose no danger to patients who have active TB and who are receiving an effective TB regimen.

Screening

Screening for latent TB infection (LTBI) is done with TST or IGRA. Indications for testing include

• Close contact with a person who has active pulmonary TB

• Chest x-ray evidence of past TB infection

• Risk factors for exposure to TB (eg, people who have immigrated within 5 yr from high-risk areas, indigent patients, IV drug users, selected US health care practitioners such as respiratory therapists and practitioners working with high-risk populations)

• Risk factors for development of active TB (eg, HIV infection or other impaired immunity, gastrectomy, jejunoileal bypass surgery, silicosis, renal insufficiency, diabetes, head or neck cancer, age > 70 yr)

• Therapeutic immunosuppression with corticosteroids, TNF inhibitors, or cancer chemotherapy

In the US, most children and other people without specific TB risk factors should not be tested to avoid false-positive reactions.

A positive TST or IGRA test result (see p. 1305 for criteria) suggests LTBI. Patients with a positive TST or IGRA result are evaluated for other risk factors and have a chest x-ray. Those with x-ray abnormalities suggesting TB require evaluation for active TB as above, including sputum examination and culture. Updated guidelines for testing and treatment of LTBI are available at the Centers for Disease Control and Prevention (CDC) web site (www.cdc.gov).

Booster reaction: Some patients with remote TB exposure, BCG vaccination, or infection with nontuberculous mycobacteria may have a negative TST or IGRA; however, the TST itself may serve as an immune booster so that a subsequent test done as little as 1 wk or as much as several years later may

be positive (booster reaction). Thus, in people who are tested regularly (eg, health care workers), the 2nd routine test will be positive, giving the false appearance of recent infection (and hence mandating further testing and treatment). If recurrent testing for LTBI is indicated, a 2nd TST should be done 1 to 4 wk after the first to identify a booster reaction (because conversion in that brief interval is highly unlikely). Subsequent TST is done and interpreted normally.

The new IGRAs for LTBI do not involve injection of antigens and thus do not cause boosting. They also are not influenced by preexisting hypersensitivity from BCG vaccination or infection with environmental mycobacteria other than *M. kansasii, M. szulgai*, and *M. marinum*.

Treatment of LTBI: Treatment is indicated principally for

• People whose TST converted from negative to positive within the previous 2 yr

• People with x-ray changes consistent with old TB and no evidence of active TB

Other indications for preventive treatment include

• People who, if infected, are at high risk of developing active TB (eg, HIV-infected people, people with drug-induced immunosuppression)

• Any child < 5 yr who is a close contact of a person with smear-positive TB, regardless of whether there was TST conversion

Other people with an incidental positive TST or IGRA but without these risk factors are often treated for LTBI, but physicians should balance individual risks of drug toxicity against the benefits of treatment.

Treatment generally consists of INH unless resistance is suspected (eg, in exposure to a known INH-resistant case). The dose is 300 mg once/day for 6 to 9 mo for most adults and 10 mg/kg for 9 mo for children. HIV-infected patients and people with abnormal chest x-rays consistent with old TB also require 9 mo of therapy. An alternative for patients resistant to or intolerant of INH is RIF 600 mg once/day for 4 mo.

The main limitations of treatment of LTBI are poor adherence and hepatotoxicity. Used for LTBI, INH causes clinical hepatitis in 1/1000 cases; hepatitis usually reverses if INH is stopped promptly. Patients being treated for LTBI should be instructed to stop the drug if they experience any new symptoms, especially unexplained fatigue, loss of appetite, or nausea. Hepatitis due to RIF is less common than with INH, but drug interactions are frequent. Monthly visits to monitor symptoms and to encourage treatment completion are standard good clinical and public health practice.

Prevention

General preventive measures (eg, staying at home, avoiding visitors, covering coughs with a tissue or hand—see p.) are followed.

Vaccination: The BCG vaccine, made from an attenuated strain of *M. bovis* is given to > 80% of the world's children, primarily in high-burden countries. Overall average efficacy is probably only 50%. However, although BCG is not believed to prevent TB infection, it reduces the rate of extrathoracic TB in children, especially TB meningitis, and therefore is considered worthwhile. BCG has few indications in the US, except unavoidable exposure of a child to an infectious TB case that cannot be effectively treated (ie, highly resistant MDR-TB) and possibly previously uninfected health care workers exposed to MDRTB or XDR-TB on a regular basis.

Although BCG vaccination often converts the TST, the reaction is usually smaller than the response to natural TB infection, and it usually wanes more quickly. The TST reaction due to BCG is rarely > 15 mm and rarely > 10 mm 15 yr after BCG administration. CDC recommends that all TST reactions in children who have had BCG be attributed to TB infection (and treated accordingly) because untreated latent infection can have serious complications. IGRAs for LTBI are not influenced by BCG vaccination.

Special Populations

Children: Primary TB in children can spread to the vertebrae (Pott's disease) or the highly vascular epiphyses of long bones. Young children may also rapidly develop serious TB, possibly miliary TB, TB meningitis, or cavitary disease, even before the TST becomes positive. However, most children have few symptoms other than a brassy cough, and the primary focus usually resolves spontaneously with or without treatment. The most common sign is hilar lymphadenopathy, but segmental atelectasis is possible. Adenopathy may progress, even after chemotherapy is started, and may cause lobar atelectasis, which usually clears during treatment. Cavitary disease is less common than in adults, and most children harbor far fewer organisms and are not infectious. Except for dosage adjustments, treatment of children is similar to that of adults (see Table 141-1).

The elderly: Reactivated disease can involve any organ, but particularly the lungs, brain, kidneys, long bones, vertebrae, or lymph nodes. Reactivation may cause few symptoms and can be overlooked for weeks or months, delaying appropriate evaluation. The frequent presence of other disorders in old age further complicates the diagnosis. At any age, recent transmission may cause apical, middle-lobe, or lower-lobe pneumonia as well as pleural effusion in previously tuberculin-negative nursing home residents. The pneumonia may not be recognized as TB and may persist and spread to other people despite broad-spectrum antibiotic treatment. In the US, miliary TB and TB meningitis, commonly thought to affect mainly young children, are more common among the elderly.

INH is hepatotoxic in up to 4 to 5% of patients > 65 yr (compared with < 1% of patients < 65 yr). In the elderly, chemoprophylaxis is indicated only if the TST increases ≥ 15 mm from a previously negative reaction. TST sensitivity can be poor in the elderly. Close contacts of an active case and others at high risk and with a negative TST or IGRA should be considered for preventive treatment unless contraindicated.

HIV-infected patients: TST sensitivity is generally poor in immunocompromised patients (who may be anergic). In some studies, IGRAs appear to perform better than the TST in immunocompromised patients, although this advantage has not yet been established.

In HIV-infected patients with LTBI, active TB develops in about 5 to 10%/yr, whereas in people who are not immunocompromised, it develops in about the same percentage over a lifetime. In the early 1990s, half of HIV-infected TB patients who were untreated or infected with an MDR strain died, with median survival of only 60 days. Now, outcomes are somewhat better in developed countries because of earlier TB diagnosis and antiretroviral therapy, but TB in HIV patients remains a serious concern. In developing countries, mortality continues to be high among patients coinfected with HIV and MDR-TB or XDR-TB.

Dissemination of bacilli during primary infection is usually much more extensive in patients with HIV infection. Consequently, a larger proportion of TB is extrapulmonary. Tuberculomas are more common and more destructive. HIV reduces both inflammatory reaction and cavitation of pulmonary lesions. As a result, a chest x-ray may show a nonspecific pneumonia or even be normal, even though AFB are present in sufficient numbers to appear on a sputum smear. Smear-negative TB is more common when HIV coinfection is present.

TB may develop early in AIDS and may be its presenting manifestation. Hematogenous dissemination of TB in patients with HIV infection causes a serious, often baffling illness with symptoms of both infections. In AIDS patients, a mycobacterial illness that develops while the CD4 count is ≥ 200/μL is almost always TB. By contrast, depending on the probability of TB exposure, a mycobacterial infection that develops while the CD4 count is < 50/μL is usually due to *M. avium* complex (see p. 1314), which is not contagious and is predominantly an infection of the blood and bone marrow, not the lungs.

TB in HIV-infected patients generally responds well to usual regimens when in vitro testing shows sensitivity. However, for MDRTB strains, outcomes are not as favorable because the drugs are more toxic and less effective. Therapy for susceptible TB should be continued for 6 to 9 mo after conversion of sputum cultures to negative but may be shortened to 6 mo if 3 separate pretreatment sputum smears are negative, suggesting a low burden of organisms. Current recommendations suggest that if the sputum

culture is positive after 2 mo of therapy, treatment is prolonged to 9 mo. HIV-infected patients whose tuberculin reactions are ≥ 5 mm (or with a positive IGRA) should receive chemoprophylaxis. Current CDC TB treatment guidelines should be consulted.

Extrapulmonary Tuberculosis

TB outside the lung usually results from hematogenous dissemination. Sometimes infection directly extends from an adjacent organ. Symptoms vary by site but generally include fever, malaise, and weight loss.

Miliary TB: Also known as generalized hematogenous TB, miliary TB occurs when a tuberculous lesion erodes into a blood vessel, disseminating millions of tubercle bacilli into the bloodstream and throughout the body. The lungs and bone marrow are most often affected, but any site may be involved. Miliary TB is most common among children < 4 yr, immunocompromised people, and the elderly.

Symptoms include fever, chills, weakness, malaise, and often progressive dyspnea. Intermittent dissemination of tubercle bacilli may lead to a prolonged FUO. Bone marrow involvement may cause anemia, thrombocytopenia, or a leukemoid reaction.

Genitourinary TB: Infection of the kidneys may manifest as pyelonephritis (eg, fever, back pain, pyuria) without the usual urinary pathogens on routine culture (sterile pyuria). Infection commonly spreads to the bladder and, in men, to the prostate, seminal vesicles, or epididymis, causing an enlarging scrotal mass. Infection may spread to the perinephric space and down the psoas muscle, sometimes causing an abscess on the anterior thigh.

Salpingo-oophoritis can occur after menarche, when the fallopian tubes become vascular. Symptoms include chronic pelvic pain and sterility or ectopic pregnancy due to tubal scarring.

TB meningitis: Meningitis often occurs in the absence of infection at other extrapulmonary sites. In the US, it is most common among the elderly and immunocompromised, but in areas where TB is common among children, TB meningitis usually occurs between birth and 5 yr. At any age, meningitis is the most serious form of TB and has high morbidity and mortality. It is the one form of TB believed to be prevented in childhood by vaccination with BCG.

Symptoms are low-grade fever, unremitting headache, nausea, and drowsiness, which may progress to stupor and coma. Kernig's and Brudzinski's signs may be positive. Stages are

1. Clear sensorium with abnormal CSF

2. Drowsiness or stupor with focal neurologic signs

3. Coma

Stroke may result from thrombosis of a major cerebral vessel. Focal neurologic symptoms suggest a tuberculous mass intracranial lesion (tuberculoma).

TB peritonitis: Peritoneal infection represents seeding from abdominal lymph nodes or from salpingo-oophoritis. Peritonitis is particularly common among alcoholics with cirrhosis.

Symptoms may be mild, with fatigue, abdominal pain, and tenderness, or severe enough to mimic acute abdomen.

TB pericarditis: Pericardial infection may develop from foci in mediastinal lymph nodes or from pleural TB. In some high-incidence parts of the world, TB pericarditis is a common cause of heart failure.

Patients may have a pericardial friction rub, pleuritic and positional chest pain, or fever. Pericardial tamponade may occur, causing dyspnea, neck vein distention, paradoxical pulse, muffled heart sounds, and possibly hypotension.

TB lymphadenitis: Usually, the hilar lymph nodes are involved. Other nodes are generally not involved unless the inoculum is large or poorly contained, allowing organisms to reach the thoracic duct, where they disseminate into the bloodstream. Most infected nodes heal, but reactivation commonly occurs. Infection in supraclavicular nodes may inoculate anterior cervical nodes, eventually resulting in scrofula (TB lymphadenitis in the neck).

Affected nodes are swollen and may be mildly tender or drain. Adjacent nodes sometimes coalesce into an irregular mass.

TB of bones and joints: Weight-bearing joints are most commonly involved, but bones of the wrist, hand, and elbow may also be affected, especially after injury.

Pott's disease is spinal infection, which begins in a vertebral body and often spreads to adjacent vertebrae, with narrowing of the disk space between them. Untreated, the vertebrae may collapse, possibly impinging on the spinal cord. Symptoms include progressive or constant pain in involved bones and chronic or subacute arthritis (usually monoarticular). In Pott's disease, spinal cord compression produces neurologic deficits, including paraplegia; paravertebral swelling may result from an abscess.

Gastrointestinal TB: Because the entire GI mucosa resists TB invasion, infection requires prolonged exposure and enormous inocula. It is very unusual in developed countries where bovine TB is rare.

Ulcers of the mouth and oropharynx may develop from eating *M. bovis*-contaminated dairy products; primary lesions may also occur in the small bowel. Intestinal invasion generally causes hyperplasia and an inflammatory bowel syndrome with pain, diarrhea, obstruction, and hematochezia. It may also mimic appendicitis. Ulceration and fistulas are possible.

TB of the liver: Liver infection is common in patients with advanced pulmonary TB and widely disseminated or miliary TB. However, the liver generally heals without sequelae when the principal infection is treated. TB in the liver occasionally spreads to the gallbladder, leading to obstructive jaundice.

Other sites: Rarely, TB may develop on abraded skin in patients with cavitary pulmonary TB. TB may infect the wall of a blood vessel and has even ruptured the aorta. Adrenal involvement, leading to Addison's disease, formerly was common but now is rare. Tubercle bacilli may spread to tendon sheaths (tuberculous tenosynovitis) by direct extension from adjacent lesions in bone or hematogenously from any infected organ.

Diagnosis

• Chest x-ray

• Tuberculin skin test

• Acid-fast stain and culture

• When available, DNA-based testing

Testing is similar to that for pulmonary TB (see p.), including chest x-ray, tuberculin skin testing (TST), and microscopic analysis (with appropriate staining) and cultures of affected body fluids (CSF, urine, or pleural, pericardial, or joint fluid) and tissue for mycobacteria. However, cultures and smears are often negative because few organisms may be present; in this case, nucleic acid amplification techniques (NAAT) may be helpful. If all tests are negative and miliary TB is still a concern, biopsies of the bone marrow and the liver are done. Blood culture results are positive in about 50% of patients with disseminated TB; such patients are often immunocompromised by HIV infection or another immunosuppressive condition. If TB is highly suspected based on other features (eg, granuloma seen on biopsy, positive TST plus unexplained lymphocytosis in pleural fluid or CSF), treatment should usually proceed despite inability to demonstrate TB organisms.

Chest x-ray may show signs of primary or active TB; in miliary TB, it shows thousands of 2- to 3-mm interstitial nodules evenly distributed through both lungs. TST and IGRA may initially be negative, but a repeat test in a few weeks is likely to be positive. If it is not, the diagnosis of TB should be questioned or causes of anergy sought.

Other imaging studies are done based on clinical findings. Abdominal or GU involvement usually requires CT or ultrasonography; renal lesions are often visible. Bone and joint involvement requires CT or MRI; MRI is preferable for spinal disease.

Body fluids typically show lymphocytosis. The most suggestive CSF constellation also includes a glucose level < 50% of that in the serum and an elevated protein level.

Treatment

Drug treatment is the most important modality and follows standard regimens and principles (see p.). Six to 9 mo of therapy is probably adequate for most sites except the meninges, which require treatment for 9 to 12 mo. Corticosteroids may help in pericarditis and meningitis (for dosing, see p.).

Surgery is required for the following:

• To drain empyema, cardiac tamponade, and CNS abscess

• To close bronchopleural fistulas

• To resect infected bowel

• To decompress spinal cord encroachment

Surgical debridement is sometimes needed in Pott's disease to correct spinal deformities or to relieve cord compression if there are neurologic deficits or pain persists; fixation of the vertebral column by bone graft is required in only the most advanced cases. Surgery is usually not necessary for TB lymphadenitis except for diagnostic purposes.

Other Mycobacterial Infections Resembling Tuberculosis

Mycobacteria other than the tubercle bacillus sometimes infect humans. These organisms are commonly present in soil and water and are much less virulent in humans than is *M. tuberculosis*. Infections with these organisms have been called atypical, environmental, and nontuberculous mycobacterial infections. Most exposures and infections by these organisms do not cause disease, which usually requires a defect in local or systemic host defenses; the frail elderly are sometimes infected. *M. avium* complex (MAC)—the closely related species of *M. avium* and *M. intracellulare*—accounts for most diseases. Other causative species are *M. kansasii, M. xenopi, M. marinum, M. ulcerans*, and the *M. fortuitum* complex (*M. fortuitum, M. abscessus*, and *M. chelonae*). Person-to-person transmission has not been documented.

The lungs are the most common site; most lung infections involve MAC but may be due to *M. kansasii, M. xenopi*, or *M. abscessus*. Occasional cases involve lymph nodes, bones and joints, the skin, and wounds. However, incidence of disseminated MAC disease is increasing in HIV-infected patients, and resistance to anti-TB drugs is the rule (except for *M. kansasii* and *M. xenopi*).

Nontuberculous mycobacterial infections are best managed by a specialist with particular expertise in that area. The American Thoracic Society publishes updated diagnostic and therapeutic guidelines on the diagnosis and management of these challenging infections.

Pulmonary disease: The typical patient is a middle-aged or older white man with previous lung problems such as chronic bronchitis, emphysema, healed TB, bronchiectasis, or silicosis. MAC also commonly causes pulmonary disease in middle-aged and elderly women with bronchiectasis, scoliosis, pectus excavatum, or mitral valve prolapse but without known underlying lung abnormalities. This syndrome appears to be increasing in frequency for unknown reasons.

Cough and expectoration are common, often associated with fatigue, weight loss, and low-grade fever. The course may be slowly progressive or stable for long periods. Respiratory insufficiency and persistent hemoptysis may develop. Fibronodular infiltrates on chest x-ray resemble those of pulmonary TB, but cavitation tends to be thin-walled, and pleural effusion is rare. So-called tree-and-bud infiltrates are also characteristic of MAC disease.

Determination of drug susceptibility may be helpful for certain organism/drug combinations but can be done only in highly specialized laboratories.

For moderately symptomatic disease due to MAC with positive sputum smears and cultures, clarithromycin 500 mg po bid or azithromycin 600 mg once/day, rifampin (RIF) 600 mg po once/day, and ethambutol (EMB) 15 to 25 mg/kg po once/day should be used for 12 to 18 mo or until cultures are negative for 12 mo. For progressive cases unresponsive to standard drugs, combinations of 4 to 6 drugs that include clarithromycin 500 mg po bid or azithromycin 600 mg once/day, rifabutin 300 mg po once/day, ciprofloxacin 250 to 500 mg po or IV bid, clofazimine 100 to 200 mg po once/day, and amikacin 10 to 15 mg/kg IV once/day may be tried. Resection surgery is recommended in exceptional cases involving well-localized disease in young, otherwise healthy patients. *M. kansasii* and *M. xenopi* infections respond to isoniazid, rifabutin, and EMB, with or without streptomycin or clarithromycin, given for 18 to 24 mo. All nontuberculous mycobacteria are resistant to pyrazinamide.

Lymphadenitis: In children 1 to 5 yr, chronic submaxillary and submandibular cervical lymphadenitis is commonly due to MAC or *M. scrofulaceum*. It is presumably acquired by oral ingestion of soil organisms.

Diagnosis is usually by excisional biopsy. Usually, excision is adequate treatment and chemotherapy is not required.

Cutaneous disease: Swimming pool granuloma is a protracted but self-limited superficial granulomatous ulcerating disease usually caused by *M. marinum* contracted from swimming in contaminated pools or from cleaning a home aquarium. *M. ulcerans* and *M. kansasii* are occasionally involved. Lesions, reddish bumps enlarging and turning purple, most frequently occur on the upper extremities or knees. Healing may occur spontaneously, but minocycline or doxycycline 100 to 200 mg po once/day, clarithromycin 500 mg po bid, or RIF plus EMB for 3 to 6 mo have been effective against *M. marinum*.

Wounds and foreign body infections: *M. fortuitum* complex has caused serious infections of penetrating wounds in the eyes and skin (especially feet) and in patients receiving contaminated materials (eg, porcine heart valves, breast implants, bone wax).

Treatment usually requires extensive debridement and removal of the foreign material. Useful drugs include imipenem 1 g IV q 6 h, levofloxacin 500 mg IV or po once/day, clarithromycin 500 mg po bid, trimethoprim/sulfamethoxazole 1 double-strength tablet po bid, doxycycline 100 to 200 mg po once/day, cefoxitin 2 g IV q 6 to 8 h, and amikacin 10 to 15 mg/kg IV once/day, for 3 to 6 mo. Combination therapy is recommended with at least 2 drugs that have in vitro activity. Infections caused by *M. abscessus* and *M. chelonae* are resistant to most antibiotics, have proved extremely difficult or impossible to cure and should be referred to an experienced specialist.

Disseminated disease: MAC causes disseminated disease commonly in patients with advanced AIDS and occasionally in those with other immunocompromised states, including organ transplantation and hairy cell leukemia. In AIDS patients, disseminated MAC usually develops late (unlike TB, which develops early), occurring simultaneously with other opportunistic infections.

Disseminated MAC disease causes fever, anemia, thrombocytopenia, diarrhea, and abdominal pain (features similar to Whipple's disease). Diagnosis can be confirmed by cultures of blood or bone marrow or by biopsy (eg, percutaneous fine-needle biopsy of liver or necrotic lymph nodes). Organisms may be identified in stool and respiratory specimens, but organisms from these specimens may represent colonization rather than true disease.

Combination therapy to clear bacteremia and alleviate symptoms usually requires 2 to 3 drugs; one is

clarithromycin 500 mg po bid or azithromycin 600 mg po once/day, plus EMB 15 to 25 mg/kg once/day. Sometimes rifabutin 300 mg once/day is also given. After successful treatment, chronic suppression with clarithromycin or azithromycin plus EMB is necessary to prevent relapse.

HIV-infected patients with a CD4 count < 100 cells/µL require prophylaxis for disseminated MAC with azithromycin 1.2 g po once/week or clarithromycin 500 mg po bid.

Leprosy

(Hansen's Disease)

Leprosy is a chronic infection caused by the acid-fast bacillus *Mycobacterium leprae*, which has a unique tropism for peripheral nerves, skin, and mucous membranes. Symptoms are myriad and include anesthetic polymorphic skin lesions and peripheral neuropathy. Diagnosis is clinical and confirmed by biopsy. Treatment is typically with dapsone plus other antimycobacterial drugs.

Because without treatment, people with leprosy are visibly disfigured and often have significant disability, they have long been feared and shunned by others. Although leprosy is not highly contagious, rarely causes death, and can be effectively treated with antibiotics, it still causes anxiety. As a result, people with leprosy and their family members often have psychologic and social problems.

Epidemiology

During 2007, > 250,000 new cases were reported. About 90% of these cases occurred in the following 8 countries (from the most cases to the least): India, Brazil, Indonesia, Congo, Bangladesh, Nigeria, Nepal, and Ethiopia. In 2006, 137 new cases were reported in the US. Cases occurred in 30 states, but more than half occurred in 6 states: California, Florida, Louisiana, Massachusetts, New York, and Texas. Most cases of leprosy in the US involve people who emigrated from developing countries.

Leprosy can develop at any age but appears most often in people aged 5 to 15 yr or > 30.

Pathophysiology

Humans are the main natural reservoir for *M. leprae*. Armadillos are the only confirmed source other than humans, although other animal and environmental sources may exist.

How leprosy is spread is unclear. It is thought to be passed from person to person through nasal droplets and secretions. Casual contact (eg, simply touching someone with the disease) and short-term contact does not seem to spread the disease. About half of people with leprosy probably contracted it through close, long-term contact with an infected person. Even after contact with the bacteria, most people do not contract leprosy; health care workers often work for many years with people who have leprosy without contracting the disease. Most (95%) immunocompetent people who are infected with *M. leprae* do not develop leprosy because of effective immunity. People who do develop leprosy probably have a poorly defined genetic predisposition.

M. leprae grow slowly (doubling in 2 wk). The usual incubation period ranges from 6 mo to 10 yr. Once infection develops, hematogenous dissemination can occur.

Classification: Leprosy can be categorized by type and number of skin areas affected:

• **Paucibacillary:** ≤ 5 skin lesions with no bacteria detected on samples from those areas

• **Multibacillary:** ≥ 6 skin lesions, bacteria detected on samples from skin lesions, or both

Leprosy can also be classified by cellular response and clinical findings:

• Tuberculoid

• Lepromatous

• Borderline

People with tuberculoid leprosy typically have a strong cell-mediated response, which limits disease to a few skin lesions (paucibacillary), and the disease is milder, less common, and less contagious. People with lepromatous or borderline leprosy typically have poor cell-mediated immunity to *M. leprae* and have more severe, systemic infection with widespread bacterial infiltration of skin, nerves, and other organs (eg, nose, testes, kidneys). They have more skin lesions (multibacillary), and the disease is more contagious.

In both classifications, the type of leprosy dictates long-term prognosis, likely complications, and duration of antibiotic treatment.

Symptoms and Signs

Symptoms usually do not begin until > 1 yr after infection (average 5 to 7 yr). Once symptoms begin, they progress slowly.

Leprosy affects mainly the skin and peripheral nerves. Nerve involvement causes numbness and weakness in areas controlled by the affected nerves.

• **Tuberculoid leprosy:** Skin lesions consist of one or a few hypoesthetic, centrally hypopigmented macules with sharp, raised borders. The rash, as in all forms of leprosy, is nonpruritic. Areas affected by this rash are numb because of damage to the underlying nerves, which may be palpably enlarged.

• **Lepromatous leprosy:** Much of the skin and many areas of the body, including the kidneys, nose, and testes, may be affected. Patients have skin macules, papules, nodules, or plaques, often symmetric. Peripheral neuropathy is more severe than in tuberculoid leprosy, with more areas of numbness; certain muscle groups may be weak. Patients may develop gynecomastia or lose eyelashes and eyebrows or digits.

• **Borderline leprosy:** Features of both tuberculoid and lepromatous leprosy are present. Without treatment, borderline leprosy may become less severe and more like the tuberculoid form, or it may worsen and become more like the lepromatous form.

Complications: The most severe complications result from the peripheral neuropathy, which causes deterioration of the sense of touch and a corresponding inability to feel pain and temperature. Patients may unknowingly burn, cut, or otherwise harm themselves. Repeated damage may lead to loss of digits. Muscle weakness can result in deformities (eg, clawing of the 4th and 5th fingers caused by ulnar nerve involvement, foot drop caused by peroneal nerve involvement).

Papules and nodules can be particularly disfiguring on the face.

Other areas of the body may be affected:

• **Feet:** Plantar ulcers with secondary infection are a major cause of morbidity, making walking painful.

• **Nose:** Damage to the nasal mucosa can result in chronic nasal congestion and nosebleeds and, if untreated, erosion and collapse of the nasal septum.

• **Eyes:** Iritis may lead to glaucoma, and corneal insensitivity may lead to scarring and blindness.

• **Sexual function:** Men with lepromatous leprosy may have erectile dysfunction and infertility. The infection can reduce testosterone and sperm production by the testes.

• **Kidneys:** Amyloidosis and consequent renal failure occasionally occur in lepromatous leprosy.

Leprosy reactions: During the course of untreated or even treated leprosy, the immune system may produce inflammatory reactions. There are 2 types.

Type 1 reactions result from a spontaneous increase in cell-mediated immunity. These reactions can cause fever and inflammation of the preexisting skin and peripheral nerve lesions, resulting in skin edema, erythema, and tenderness and worsening nerve function. These reactions, particularly if not treated early, contribute significantly to nerve damage. Because the immune response is increased, these reactions are termed reversal reactions, despite the apparent clinical worsening.

Type 2 reactions (erythema nodosum leprosum, or ENL) are systemic inflammatory reactions that appear to be a vasculitis or panniculitis and probably involve circulating immune complex deposition or increased T-helper cell function. They have become less common since clofazimine was added to the drug regimen. Patients may develop erythematous and painful papules or nodules that may pustulate and ulcerate and cause fever, neuritis, lymphadenitis, orchitis, arthritis (particularly in large joints, usually knees), and glomerulonephritis. Hemolysis or bone marrow suppression may cause anemia, and hepatic inflammation may cause mild abnormalities in liver function tests.

Diagnosis

• Microscopic examination of skin biopsy specimen

Diagnosis is suggested by the clinical picture of skin lesions and peripheral neuropathy and confirmed by microscopic examination of biopsy specimens; the organism does not grow on artificial culture media. Biopsy specimens should be taken from the advancing edge of tuberculoid lesions or, in lepromatous leprosy, from nodules or plaques.

Serum IgM antibodies to *M. leprae* are specific but insensitive (present in only two thirds of patients with tuberculoid leprosy). Diagnostic usefulness is further limited in endemic areas because such antibodies may be present in asymptomatic infection.

Treatment

• Long-term, multidrug regimens with dapsone, rifampin, and sometimes clofazimine

• Sometimes lifelong maintenance antibiotics

Antibiotics can stop the progression of leprosy but do not reverse any nerve damage or deformity. Thus, early detection and treatment are vitally important. Because of antibiotic resistance, multidrug regimens are used. The drugs chosen depend on the type of leprosy; multibacillary leprosy requires more intensive regimens and a longer duration than paucibacillary does. Advice about diagnosis and treatment is available from the National Hansen's Disease Program in Baton Rouge, LA (1-800-642-2477). Standard regimens recommended by the WHO differ somewhat from those used in the US.

Multibacillary: The standard WHO regimen includes dapsone, rifampin, and clofazimine. Patients take rifampin 600 mg and clofazimine 300 mg po once/mo under a health care practitioner's supervision and dapsone 100 mg plus clofazimine 50 mg once/day without supervision. This regimen is continued for 12 to 24 mo, depending on disease severity.

In the US, the regimen is rifampin 600 mg po once/day and dapsone 100 mg po once/day for 3 yr. Dapsone is continued indefinitely for lepromatous leprosy and for 10 yr for borderline leprosy.

Paucibacillary: In the standard WHO regimen, patients take rifampin 600 mg po once/mo with supervision and dapsone 100 mg once/day without supervision for 6 mo. People who have only a single skin lesion are given a single dose of rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg.

In the US, the regimen is rifampin 600 mg po once/day and dapsone 100 mg po once/day for 6 mo. Dapsone is continued for 3 yr for indeterminate and tuberculoid leprosy and for 5 yr for borderline

tuberculoid.

Drugs for leprosy: Dapsone is relatively inexpensive and generally safe to use. Adverse effects include hemolysis and anemia (which are generally mild) and allergic dermatoses (which can be severe); rarely, dapsone syndrome (exfoliative dermatitis, high fever, mononucleosis-like WBC differential) occurs.

Rifampin, is primarily bactericidal for *M. leprae* and is even more effective than dapsone. However, if given at the recommended US dosage of 600 mg po once/day, it is too expensive for many developing countries. Adverse effects include hepatotoxicity, flu-like syndromes, and, rarely, thrombocytopenia and renal failure.

Clofazimine is extremely safe. The main side effect is temporary skin pigmentation.

Leprosy reactions: Patients with type 1 reactions (except minor skin inflammation) are given prednisone 40 to 60 mg po once/day initially, followed by low maintenance doses (often as low as 10 to 15 mg once/day) for a few months. Minor skin inflammation should not be treated.

First and 2nd episodes of ENL may be treated, if mild, with aspirin or, if significant, with 1 wk of prednisone 40 to 60 mg po once/day plus antimicrobials. For recurrent cases, thalidomide 100 to 300 mg po once/day is the drug of choice (in the US, available through the National Hansen's Disease Program). However, because of its teratogenicity, thalidomide should not be given to women who may become pregnant. Adverse effects are mild constipation, mild leukopenia, and sedation.

Prevention

Because leprosy is not very contagious, risk of spread is low. Only the untreated lepromatous form is contagious, but even then the infection is not easily spread. Once treatment has begun, leprosy cannot be spread. Avoiding contact with bodily fluids from and the rash on infected people is the best prevention.

The BCG vaccine, used to prevent TB, provides some protection against leprosy but is not often used.

Chapter 142. Fungi

Introduction

(See also Ch. 82.)

Fungal infections are often classified as opportunistic or primary. Opportunistic infections are those that develop mainly in immunocompromised hosts; primary infections can develop in immunocompetent hosts. Fungal infections can be systemic or local. Local fungal infections typically involve the skin (see p. 703), mouth (see p. 509), and vagina (see p. 2544) and may occur in normal or immunocompromised hosts.

Opportunistic fungal infections: Many fungi are opportunists and are usually not pathogenic except in an immunocompromised host. Causes of immunocompromise include AIDS, azotemia, diabetes mellitus, bronchiectasis, emphysema, TB, lymphoma, leukemia, other hematologic cancers, burns, and therapy with corticosteroids, immunosuppressants, or antimetabolites. Patients who spend more than several days in an ICU can become compromised because of medical procedures, underlying disorders, and undernutrition.

Typical opportunistic systemic fungal infections (mycoses) include

• Candidiasis

• Aspergillosis

• Mucormycosis (zygomycosis)

• Fusariosis

Systemic mycoses affecting severely immunocompromised patients often manifest acutely with rapidly progressive pneumonia, fungemia, or manifestations of extrapulmonary dissemination.

Primary fungal infections: These infections usually result from inhalation of fungal spores, which can cause a localized pneumonia as the primary manifestation of infection. In immunocompetent patients, systemic mycoses typically have a chronic course; disseminated mycoses with pneumonia and septicemia are rare and, if lung lesions develop, usually progress slowly. Months may elapse before medical attention is sought or a diagnosis is made. Symptoms are rarely intense in such chronic mycoses, but fever, chills, night sweats, anorexia, weight loss, malaise, and depression may occur. Various organs may be infected, causing symptoms and dysfunction.

Primary fungal infections may have a characteristic geographic distribution, which is especially true for the endemic mycoses caused by certain dimorphic fungi. For example,

• **Coccidioidomycosis:** Confined primarily to the southwestern US and northern Mexico

• **Histoplasmosis:** Occurring primarily in the eastern and Midwestern US

• **Blastomycosis:** Confined to North America and Africa

• **Paracoccidioidomycosis (formerly, South American blastomycosis):** Confined to that continent

However, travelers can manifest disease any time after returning from endemic areas.

When fungi disseminate from a primary focus in the lung, the manifestations may be characteristic, as for the following:

• **Cryptococcosis:** Usually, chronic meningitis

• **Progressive disseminated histoplasmosis:** Generalized involvement of the reticuloendothelial

system (liver, spleen, bone marrow)

• **Blastomycosis:** Single or multiple skin lesions or involvement of the prostate

Diagnosis

• Cultures and stains (typically for fungi and mycobacteria)

• Sometimes serologic tests (mainly for *Aspergillus, Candida, Coccidioides*, and *Cryptococcus*)

• Rarely biopsy

If clinicians suspect an acute or a chronic primary fungal infection, they should obtain a detailed travel and residential history to determine whether patients may have been exposed to certain endemic mycoses, perhaps years previously.

Pulmonary fungal infections must be distinguished from TB, tumors, and chronic pneumonias caused by nonfungal organisms. Specimens are obtained for fungal and acid-fast bacilli culture and histopathology. Sputum samples may be adequate, but occasionally bronchoalveolar lavage, transthoracic needle biopsy, or even surgery may be required to obtain an acceptable specimen.

Fungi that cause primary systemic infections are readily recognized by their histopathologic appearance. However, identifying the specific fungus may be difficult and usually requires fungal culture. The clinical significance of positive sputum cultures may be unclear if they show commensal organisms (eg, *Candida albicans*) or fungi ubiquitous in the environment (eg, *Aspergillus* sp). Therefore, evidence of tissue invasion is required for a diagnosis of candidiasis, aspergillosis, or other opportunistic fungal infections (eg, fusariosis, pseudallescheriasis) because these fungi may not be causing the symptoms.

Serologic tests may be used to check for many systemic mycoses if culture and histopathology are unavailable or unrevealing, although few provide definitive diagnoses. Particularly useful tests include the following:

• Measurement of organism-specific antigens, most notably from *Cryptococcus neoformans, Histoplasma capsulatum*, and *Aspergillus* sp

• Measurement of histoplasmin in urine to diagnose histoplasmosis

• Complement fixation assays and newer enzyme immunoassays for anticoccidioidal antibodies, which are satisfactorily specific and do not require proof of rising levels (high titers confirm the diagnosis and indicate high risk of extrapulmonary dissemination)

• Detection of antibodies in CSF of patients with chronic meningitis to confirm the diagnosis

Most other tests for antifungal antibodies have low sensitivity, specificity, or both and, because measurement of acute and convalescent titers is required, cannot be used to guide initial therapy.

Antifungal Drugs

Drugs for systemic antifungal treatment include amphotericin B (and its lipid formulations), various azole derivatives, echinocandins, and flucytosine (see
Table 142-1).

[**Table 142-1.** Some Drugs for Systemic Fungal Infections]

Amphotericin B, an effective but relatively toxic drug, has long been the mainstay of antifungal therapy for invasive and serious mycoses. However, newer potent and less toxic triazoles and echinocandins are now often recommended as first-line drugs for many invasive fungal infections. These drugs have markedly changed the approach to antifungal therapy, sometimes even allowing oral treatment of chronic

mycoses.

Amphotericin B

Amphotericin B has been the mainstay of antifungal therapy for invasive and serious mycoses, but other antifungals (eg, voriconazole, posaconazole, the echinocandins) are now considered first-line drugs for many of these infections.

For **chronic mycoses**, conventional amphotericin B is usually started at ≥ 0.3 mg/kg IV once/day, increased as tolerated to the desired dose (0.4 to 1.0 mg/kg; generally not > 50 mg/day); many patients tolerate the target dose on the first day. If patients tolerate the target dose, twice that dose can be given on a more convenient alternate-day schedule. Extended treatment courses may be even less frequent (eg, 3 times/wk).

For **acute, life-threatening mycoses**, amphotericin B is started at 0.6 to 1.0 mg/kg IV once/day. For certain rapidly progressive opportunistic mycoses (eg, invasive aspergillosis), daily doses as high as 1.5 mg/kg have been used, usually divided into 2 or 3 infusions. These doses must be decreased to about 0.5 mg/kg/day as nephrotoxicity develops.

For **chronic meningitis,** intrathecal amphotericin B injections can be used but are now rarely needed because potent triazoles (eg, voriconazole, posaconazole) are an effective alternative. Administration is usually via direct intracisternal injection or through a subcutaneous Ommaya-type reservoir connected to an intraventricular catheter. Headache, nausea, and vomiting may occur, but adding dexamethasone to each intrathecal injection may lessen these effects. Amphotericin B can also be given as lumbar intrathecal injections. At the time of injection, ≥ 10 mL of CSF is withdrawn into a syringe containing amphotericin B diluted in 5% D/W to 0.2 mg/mL. Doses of 0.05 to 0.5 mg are then injected over 2 min or more. Doses are gradually increased as tolerated, peaking with a regimen of 0.5 mg 3 times/wk.

Formulations: There are 2 formulations of amphotericin:

• Standard (conventional)

• Lipid-based

The **standard formulation**, colloidal amphotericin B deoxycholate, must always be given in 5% D/W because salts can precipitate the drug. It is usually given over 2 to 3 h, although more rapid infusions over 20 to 60 min can be used in selected patients. However, more rapid infusions usually have no advantage. Many patients experience chills, fever, nausea, vomiting, anorexia, headache, and, occasionally, hypotension during and for several hours after an infusion. Amphotericin B may also cause chemical thrombophlebitis when given via peripheral veins. Pretreatment with acetaminophen or NSAIDs is often used; if these drugs are ineffective, hydrocortisone 25 to 50 mg or diphenhydramine 25 mg is sometimes added to the infusion or given as a separate IV bolus. Often, hydrocortisone can be tapered and omitted during extended therapy. Severe chills and rigors can be relieved or prevented by meperidine 50 to 75 mg IV.

Several **lipid vehicles** reduce the toxicity of amphotericin B (particularly nephrotoxicity and infusion-related symptoms). Three preparations are available:

• Amphotericin B lipid complex

• Liposomal amphotericin B

• Amphotericin B cholesteryl sulfate

The first 2 lipid formulations are preferred over conventional amphotericin B because they cause fewer infusion-related symptoms and less nephrotoxicity. Amphotericin B cholesteryl sulfate does not provide any advantages over conventional amphotericin B.

Adverse effects: The main adverse effects are

• Nephrotoxicity (most common)

• Bone marrow suppression

Renal impairment is the major toxic risk of amphotericin B therapy. Serum creatinine and BUN should be monitored before treatment and at regular intervals during treatment: several times/wk for the first 2 to 3 wk, then 1 to 4 times/mo as clinically indicated. Amphotericin B is unique among nephrotoxic antimicrobial drugs because it is not eliminated appreciably via the kidneys and does not accumulate as renal failure worsens. Nevertheless, dosages should be lowered if serum creatinine rises to > 3.0 to 3.5 mg/dL (> 265 to 309 μmol/L) or BUN rises to > 50 mg/dL (> 18 mmol urea/L). Acute nephrotoxicity can be reduced by aggressive IV hydration with saline before amphotericin B infusion; at least 1 L of normal saline should be given before amphotericin infusion. Mild to moderate renal function abnormalities induced by amphotericin B usually resolve gradually after therapy is completed. Permanent damage occurs primarily after prolonged treatment; after > 4 g total dose, about 75% of patients have persistent renal insufficiency.

Amphotericin B also frequently suppresses bone marrow function, manifested primarily by anemia. Hepatotoxicity or other untoward effects are unusual.

Azole Antifungals

Azoles block the synthesis of ergosterol, an important component of the fungal cell membrane. They can be given orally to treat chronic mycoses. The first such oral drug, ketoconazole, has largely been supplanted by more effective, less toxic triazole derivatives, such as fluconazole, itraconazole, posaconazole, and voriconazole. Drug interactions can occur with all azoles but are less likely with fluconazole.

Fluconazole: This water-soluble drug is absorbed almost completely after an oral dose. It is excreted largely unchanged in urine and has a half-life of > 24 h, allowing single daily doses. It has high penetration into CSF (≥ 70% of serum levels) and has been especially useful in treating cryptococcal and coccidioidal meningitis. It is also one of the first-line drugs for treatment of candidemia in non-neutropenic patients. Doses range from 200 to 400 mg po once/day to as high as 160 mg once/day in some seriously ill patients and in patients infected with *Candida glabrata* or other *Candida* sp (not *C. albicans*); daily doses of ≥ 1000 mg have been given and had acceptable toxicity.

Adverse effects that occur most commonly are GI discomfort and skin rash. More severe toxicity is unusual, but the following have occurred: hepatic necrosis, Stevens-Johnson syndrome, anaphylaxis, alopecia, and, when taken after the 1st trimester of pregnancy, congenital fetal anomalies.

Drug interactions occur less often with fluconazole than with other azoles. However, fluconazole sometimes elevates serum levels of cyclosporine, rifabutin, phenytoin, tacrolimus, warfarin-type oral anticoagulants, sulfonylurea drugs (eg, tolbutamide), and zidovudine. Rifampin may lower fluconazole blood levels.

Itraconazole: This drug has become the standard treatment for lymphocutaneous sporotrichosis as well as for mild or moderately severe histoplasmosis, blastomycosis, and paracoccidioidomycosis. It is also effective in mild cases of invasive aspergillosis, some cases of coccidioidomycosis, and certain types of chromoblastomycosis. Itraconazole can clear some types of fungal meningitis, but it is not the drug of choice. Because of its high lipid solubility and protein binding, itraconazole blood levels tend to be low, but tissue levels are typically high. Drug levels are negligible in urine and CSF. Use of itraconazole is likely to decline as use of voriconazole and posaconazole increases.

Adverse effects with doses of up to 400 mg/day most commonly are GI, but a few men have reported erectile dysfunction, and higher doses may cause hypokalemia, hypertension, and edema. Other reported adverse effects include allergic rash, hepatitis, and hallucinations.

Drug and food interactions can be significant. Acidic drinks (eg, cola, acidic fruit juices) or food

(especially high-fat foods) improves absorption from the GI tract. However, absorption may be reduced if itraconazole is taken with prescription or OTC drugs used to lower gastric acidity. Several drugs, including rifampin, rifabutin, didanosine, phenytoin, and carbamazepine, may decrease serum itraconazole levels. Itraconazole also inhibits metabolic degradation of other drugs, elevating blood levels with potentially serious consequences. Serious, even fatal cardiac arrhythmias may occur if itraconazole is used with cisapride (not available in the US) or some antihistamines (eg, terfenadine, astemizole, perhaps loratadine). Rhabdomyolysis has been associated with itraconazole-induced elevations in blood levels of cyclosporine or statins. Blood levels of digoxin, tacrolimus, oral anticoagulants, or sulfonylureas may increase when these drugs are used with itraconazole.

Posaconazole: The triazole posaconazole is an oral suspension; it is not available in tablet or IV formulations. This drug is highly active against yeasts and molds and effectively treats various opportunistic mold infections, such as those due to dematiaceous (dark-walled) fungi (eg, *Cladophialophora* sp). Posaconazole is also being evaluated as prophylaxis in neutropenic patients with various cancers.

Adverse effects for posaconazole, as for other triazoles, include a prolonged QT interval and interaction with many drugs, including rifampin, statins, various immunosuppressants, and barbiturates.

Voriconazole: This broad-spectrum triazole can be used as first-line therapy for serious *Aspergillus* infections; most clinical mycologists consider it the treatment of choice for *Aspergillus* infections in immunocompetent and immunocompromised hosts. Voriconazole can also be used to treat *Scedosporium apiospermum* and *Fusarium* infections. Additionally, the drug is effective in candidal esophagitis and other candidal infections; it has activity against a broader spectrum of *Candida* sp than does fluconazole.

Adverse effects that must be monitored for include hepatotoxicity, visual disturbances, hallucinations, and dermatologic reactions. This drug can prolong the QT interval. Also, there are numerous drug-drug interactions, notably with certain immunosuppressants used after organ transplantation.

Echinocandins

Echinocandins are water-soluble lipopeptides that inhibit glucan synthase. Their mechanism of action is unique among antifungal drugs; echinocandins target the fungal cell wall, making them attractive because they lack cross-resistance with other drugs and their target is fungal and has no mammalian counterpart. Echinocandins available in the US are anidulafungin, caspofungin, and micafungin. There is little evidence to suggest that one is better than the other, but anidulafungin appears to interact with fewer drugs than the other two.

These drugs can be used to treat various forms of candidiasis, aspergillosis, and other mycoses.

Flucytosine

Flucytosine, a nucleic acid analog, is water soluble and well absorbed after oral administration. Preexisting or emerging resistance is common, so it is almost always used with another antifungal, usually amphotericin B. Flucytosine plus amphotericin B is used primarily to treat cryptococcosis but is also valuable for some cases of disseminated candidiasis, other yeast infections, and severe invasive aspergillosis. Flucytosine plus antifungal azoles may be beneficial in treating cryptococcosis and some other mycoses.

The usual dose (12.5 to 37.5 mg/kg po qid) leads to high drug levels in serum, urine, and CSF. Major adverse effects are bone marrow suppression (thrombocytopenia and leukopenia), hepatotoxicity, and enterocolitis; only degree of bone marrow suppression is proportional to serum levels. Because flucytosine is cleared primarily by the kidneys, blood levels rise if nephrotoxicity develops during concomitant use with amphotericin B, particularly when amphotericin B is used in doses > 0.4 mg/kg/day. Flucytosine serum levels should be monitored, and the dosage should be adjusted to keep levels between 40 and 90 µg/mL. CBC and renal and liver function tests should be done twice/wk. If blood levels are unavailable, therapy is begun at 25 mg/kg qid, and dosage is decreased if renal function deteriorates.

Aspergillosis

Aspergillosis is an opportunistic infection caused by inhaling spores of the mold *Aspergillus*; the spores invade blood vessels, causing hemorrhagic necrosis and infarction. Symptoms may be those of asthma, pneumonia, sinusitis, or rapidly progressing systemic illness. Diagnosis is primarily clinical but may be aided by imaging, histopathology, and specimen staining and culture. Treatment is with voriconazole, amphotericin B (or its lipid formulations), caspofungin, itraconazole, or flucytosine. Fungus balls may require surgical resection. Recurrence is common.

Aspergillus sp are among the most common environmental molds, frequently present in or on the following:

• Decaying vegetation (eg, compost heaps)

• Insulating materials

• Air conditioning or heating vents

• Operating pavilions and patient rooms

• Hospital implements

• Airborne dust

Pathophysiology

Invasive infections are usually acquired by inhalation of spores or, occasionally, by direct invasion through damaged skin.

Major risk factors include

• Neutropenia

• Long-term high-dose corticosteroid therapy

• Organ transplantation (especially bone marrow transplantation)

• Hereditary disorders of neutrophil function (eg, chronic granulomatous disease)

• AIDS

Aspergillus sp tends to infect open spaces, such as pulmonary cavities caused by previous lung disorders (eg, bronchiectasis, tumor, TB), the sinuses, or ear canals (otomycosis). Such infections tend to be locally invasive and destructive, although systemic spread sometimes occurs, particularly in immunocompromised patients.

A. fumigatus is the most common cause of invasive pulmonary disease; *A. flavus* most often causes invasive extrapulmonary disease, probably because these patients are more severely immunosuppressed than patients infected with *A. fumigatus*.

Focal infections, typically in the lung, sometimes form a fungus ball (aspergilloma), a characteristic growth of tangled masses of hyphae, with fibrin exudate and few inflammatory cells, typically encapsulated by fibrous tissue. Occasionally, there is some local invasion of tissue at the periphery of the cavity, but usually the fungus just resides within the cavity with no appreciable local invasion.

A chronic form of invasive aspergillosis occasionally occurs, particularly in patients with chronic

granulomatous disease, which is characterized by a hereditary phagocytic cell defect. *Aspergillus* sp can also cause endophthalmitis after trauma or surgery to the eye (or by hematogenous seeding) and infections of intravascular and intracardiac prostheses.

Primary superficial aspergillosis is uncommon but may occur in burns; beneath occlusive dressings; after corneal trauma (keratitis); or in the sinuses, mouth, nose, or ear canal.

Allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to *A. fumigatus* that results in lung inflammation unrelated to fungal invasion of tissues (see p.).

Symptoms and Signs

Chronic pulmonary aspergillosis causes cough, often with hemoptysis and shortness of breath. If untreated, invasive pulmonary aspergillosis usually causes rapidly progressive, ultimately fatal respiratory failure.

Extrapulmonary invasive aspergillosis begins with skin lesions, sinusitis, or pneumonia and may involve the liver, kidneys, brain, and other tissues; it is often rapidly fatal.

Aspergillosis in the sinuses can form an aspergilloma or cause allergic fungal sinusitis or a chronic, slowly invasive granulomatous inflammation with fever, rhinitis, and headache. Patients may have necrosing cutaneous lesions overlying the nose or sinuses, palatal or gingival ulcerations, signs of cavernous sinus thrombosis, or pulmonary or disseminated lesions.

Diagnosis

• Usually fungal culture and histopathology of tissue samples

Because *Aspergillus* sp are common in the environment, positive sputum cultures may be due to environmental contamination or noninvasive colonization in patients with chronic lung disease; positive cultures are significant mainly when obtained from patients with increased susceptibility due to immunosuppression or when there is high suspicion due to typical imaging findings. Conversely, sputum cultures from patients with aspergillomas or invasive pulmonary aspergillosis are often negative because cavities are often walled off from airways and because invasive disease progresses mainly by vascular invasion and tissue infarction.

Chest x-rays are taken, and CT of sinuses is done if sinus infection is suspected. A movable fungus ball within a cavitary lesion is characteristic on both, although most lesions are focal and solid. Sometimes imaging detects a halo sign (a thin air shadow surrounding a nodule), representing cavitation within a necrotic lesion. Diffuse, generalized pulmonary infiltrates are seen in some patients.

Culture and histopathology of a tissue sample are usually necessary for confirmation; the sample is typically taken from the lungs via bronchoscopy and from the sinuses via anterior rhinoscopy. Because cultures take time and histopathology results may be false-negative, most decisions to treat are based on strong presumptive clinical evidence. Large vegetations often release sizable emboli that may occlude blood vessels and provide specimens for diagnosis.

Various serologic assays exist but are of limited value for rapid diagnosis of acute, life-threatening invasive aspergillosis. Detection of antigens such as galactomannans can be specific but is not sufficiently sensitive to identify most cases in their early stages. Blood cultures are almost always negative, even in rare cases of endocarditis.

Treatment

• Voriconazole or amphotericin B

• Sometimes surgery for aspergillomas

Invasive infections usually require aggressive treatment with IV amphotericin B or voriconazole (generally considered the first-choice drug). Oral itraconazole (but not fluconazole) can be effective in some cases. Caspofungin or other echinocandins may be used as salvage therapy. Combination therapy with azoles and echinocandins or with amphotericin B and echinocandins has been effective in some patients.

Usually, complete cure requires reversal of immunosuppression (eg, resolution of neutropenia, discontinuation of corticosteroids). Recrudescence is common if neutropenia recurs.

Aspergillomas neither require nor respond to systemic antifungal therapy but may require resection because of local effects, especially hemoptysis.

Blastomycosis

(Gilchrist's Disease; North American Blastomycosis)

Blastomycosis is a pulmonary disease caused by inhaling spores of the dimorphic fungus *Blastomyces dermatitidis*; occasionally, the fungi spread hematogenously, causing extrapulmonary disease. Symptoms result from pneumonia or from dissemination to multiple organs, most commonly the skin. Diagnosis is clinical, by chest x-ray, or both and is confirmed by laboratory identification of the fungi. Treatment is with itraconazole, fluconazole, or amphotericin B.

In North America, the endemic area for blastomycosis includes

• Ohio-Mississippi River valleys (extending into the middle Atlantic and Southeastern states)

• Northern Midwest

• Upstate New York

• Southern Canada

Infection also occurs in the Middle East and Africa.

Immunocompetent people can contract this infection. Although blastomycosis may be more common and more severe in immunocompromised patients, it is a less common opportunistic infection than histoplasmosis or coccidioidomycosis.

B. dermatitidis grows as a mold at room temperature in soil enriched with animal excreta and in moist, decaying, acidic organic material, often near rivers. In the lungs, inhaled spores convert into large (15 to 20 μm) invasive yeasts, which form characteristic broad-based buds.

Once in the lungs, infection may

• Remain localized in the lungs

• Disseminate hematogenously

Hematogenous dissemination can cause focal infection in numerous organs, including the skin, prostate, epididymides, testes, kidneys, vertebrae, ends of long bones, subcutaneous tissues, brain, oral or nasal mucosa, thyroid, lymph nodes, and bone marrow.

Symptoms and Signs

Pulmonary: Pulmonary blastomycosis may be asymptomatic or cause an acute, self-limited disease that often goes unrecognized. It can also begin insidiously and develop into a chronic, progressive infection. Symptoms include a productive or dry hacking cough, chest pain, dyspnea, fever, chills, and drenching

sweats.

Pleural effusion occurs occasionally. Some patients have rapidly progressive infections, and acute respiratory distress syndrome may develop.

Extrapulmonary: In extrapulmonary disseminated blastomycosis, symptoms depend on the organ involved. Skin lesions are by far the most common; they may be single or multiple and may occur with or without clinically apparent pulmonary involvement. Papules or papulopustules usually appear on exposed surfaces and spread slowly. Painless miliary abscesses, varying from pinpoint to 1 mm in diameter, develop on the advancing borders. Irregular, wartlike papillae may form on surfaces. As lesions enlarge, the centers heal, forming atrophic scars. When fully developed, an individual lesion appears as an elevated verrucous patch, usually ≥ 2 cm wide with an abruptly sloping, purplish red, abscess-studded border. Ulceration may occur if bacterial superinfection is present.

If bone lesions develop, overlying areas are sometimes swollen, warm, and tender. Genital lesions cause painful epididymal swelling, deep perineal discomfort, or prostatic tenderness detected during rectal examination.

Diagnosis

• Chest x-ray

• Fungal cultures

A chest x-ray should be taken. Focal or diffuse infiltrates may be present, sometimes as patchy bronchopneumonia fanning out from the hilum. These findings must be distinguished from other causes of pneumonia (eg, other mycoses, TB, tumors). Skin lesions can be mistaken for sporotrichosis, TB, iodism, or basal cell carcinoma. Genital involvement may mimic TB.

Cultures of infected material are done; they are definitive when positive. The organism's characteristic appearance, seen during microscopic examination of tissues or sputum, is also frequently diagnostic. Serologic testing is not sensitive but is useful if positive.

Treatment

• For mild to moderate disease, itraconazole

• For severe, life-threatening infection, amphotericin B

Untreated blastomycosis is usually slowly progressive and is rarely ultimately fatal. Treatment depends on severity of the infection. For mild to moderate disease, itraconazole 200 to 400 mg po once/day is used. Fluconazole appears less effective, but 400 to 800 mg po once/day may be tried in itraconazole-intolerant patients with mild disease. For severe, life-threatening infections, IV amphotericin B is usually effective.

Voriconazole and posaconazole are highly active against *B. dermatitidis*, but their role has not yet been defined.

Candidiasis (Invasive)

(Candidosis; Moniliasis)

(See also pp. 703, 1102, and 2544.)

Candidiasis is infection by *Candida* sp (most often *C. albicans*), manifested by mucocutaneous lesions, fungemia, and sometimes focal infection of multiple sites. Symptoms depend on the site of infection and include dysphagia, skin and mucosal lesions, blindness, vaginal symptoms (itching, burning, discharge), fever, shock, oliguria, renal shutdown, and disseminated intravascular coagulation. Diagnosis is confirmed by histopathology and cultures from normally

sterile sites. Treatment is with amphotericin B, fluconazole, echinocandins, voriconazole, or posaconazole.

Candida sp are commensal organisms that inhabit the GI tract and sometimes the skin (see p.). Unlike other systemic mycoses, candidiasis results from endogenous organisms. Most infections are caused by *C. albicans* or *C. tropicalis*; however, *C. glabrata* (formerly *Torulopsis glabrata*) is increasingly involved in fungemia, UTIs, and, occasionally, pneumonia or other focal disease.

Candida sp account for about 80% of major systemic fungal infections and are the most common cause of fungal infections in immunocompromised patients. Candidal infections are one of the most common hospital-acquired infections.

Candidiasis involving the mouth and esophagus is a defining opportunistic infection in AIDS. Although mucocutaneous candidiasis is frequently present in HIV-infected patients, hematogenous dissemination is unusual until immunosuppression becomes profound. Neutropenic patients (eg, those receiving cancer chemotherapy) are at high risk of developing life-threatening disseminated candidiasis.

Candidemia may occur in nonneutropenic patients during prolonged hospitalization. This bloodstream infection is often related to one or more of the following:

• Multiple trauma

• Surgical procedures

• Multiple courses of broad-spectrum antibacterial therapy

• IV hyperalimentation

IV lines and the GI tract are the usual portals of entry. Candidemia often prolongs hospitalization and increases mortality due to concurrent disorders. Prolonged or untreated candidemia may lead to endocarditis or meningitis as well as to focal involvement of skin, subcutaneous tissues, bones, joints, liver, spleen, kidneys, eyes, and other tissues. Endocarditis is commonly related to IV drug abuse, valve replacement, or intravascular trauma induced by indwelling IV catheters.

All forms of disseminated candidiasis should be considered serious, progressive, and potentially fatal.

Symptoms and Signs

Esophagitis is most often manifested by dysphagia. Symptoms of respiratory tract infections (eg, cough) are nonspecific.

Candidemia usually causes fever, but no symptoms are specific. Some patients develop a syndrome resembling bacterial sepsis, with a fulminating course that may include shock, oliguria, renal shutdown, and disseminated intravascular coagulation.

Candidal endophthalmitis starts as white retinal lesions that are initially asymptomatic but can progress, opacifying the vitreous and causing potentially irreversible scarring and blindness. In neutropenic patients, retinal hemorrhages occasionally also occur, but actual infection of the eye is rare.

Papulonodular skin lesions may also develop, especially in neutropenic patients, in whom they indicate widespread hematogenous dissemination to other organs. Symptoms of other focal infection depend on the organ involved.

Diagnosis

• Histopathology and fungal cultures

Because *Candida* spp are commensal, their culture from sputum, the mouth, the vagina, urine, stool, or

skin does not necessarily signify an invasive, progressive infection. A characteristic clinical lesion must also be present, histopathologic evidence of tissue invasion (eg, yeasts, pseudohyphae, or hyphae in tissue specimens) must be documented, and other etiologies must be excluded. Positive cultures of blood, CSF, pericardium or pericardial fluid or tissue biopsy specimens provide definitive evidence that systemic therapy is needed.

Serologic assays do not have sufficient specificity or sensitivity to be useful.

Treatment

• Amphotericin B for severe illness, otherwise an echinocandin or azole

Predisposing conditions (eg, neutropenia, immunosuppression, use of broad-spectrum antibacterial antibiotics, hyperalimentation, presence of indwelling lines) should be reversed or controlled if possible. IV amphotericin B is recommended for most severely ill patients, especially those who are immunosuppressed. Echinocandins are an alternative to amphotericin B in adults with or without neutropenia. Fluconazole 400 to 800 mg po once/day is also considered a first-line drug (unless *C. krusei* or *C. glabrata* is involved) for nonneutropenic patients and may be effective in patients with neutropenia.

Esophageal candidiasis is treated with fluconazole 200 to 400 mg po or IV once/day or itraconazole 200 mg po once/day. If these drugs are ineffective or if infection is severe, voriconazole 4 mg/kg po or IV bid, posaconazole 400 mg po bid, or one of the echinocandins may be used. These drugs are also effective for bloodstream and other hematogenously disseminated infections.

Coccidioidomycosis

(San Joaquin Fever; Valley Fever)

Coccidioidomycosis is a pulmonary or hematogenously spread disseminated disease caused by the fungus *Coccidioides immitis*; it usually occurs as an acute benign asymptomatic or self-limited respiratory infection. The organism occasionally disseminates to cause focal lesions in other tissues. Symptoms, if present, are those of lower respiratory infection or low-grade nonspecific disseminated disease. Diagnosis is suspected based on clinical and epidemiologic characteristics and confirmed by chest x-ray, culture, and serologic testing. Treatment, if needed, is usually with fluconazole, itraconazole, newer triazoles, or amphotericin B.

In North America, the endemic area for coccidioidomycosis includes

• The southwestern US

• Northern Mexico

The affected areas of the southwestern US include Arizona, the central valley of California, parts of New Mexico, and Texas west of El Paso. The area extends into northern Mexico, and foci occur in parts of Central America and Argentina.

Pathophysiology

Infections are acquired by inhaling spore-laden dust. Because of travel and delayed onset of clinical manifestations, infections can become evident outside endemic areas.

Once inhaled, *C. immitis* spores convert to large tissue-invasive spherules. As spherules enlarge and then rupture, each releases thousands of small endospores, which may form new spherules. Pulmonary disease is characterized by an acute, subacute, or chronic granulomatous reaction with varying degrees of fibrosis. Lesions may cavitate or form nodular-like coin lesions.

Sometimes disease progresses, with widespread lung involvement, dissemination, or both; focal lesions may form in almost any other tissue, most commonly in skin, subcutaneous tissues, bones (osteomyelitis),

and meninges (meningitis). Progressive disease is more common among men and is more likely to occur in the following contexts:

• HIV infection

• Use of immunosuppressants

• Advanced age

• 2nd half of pregnancy or postpartum

• Certain ethnic backgrounds (Filipino, African American, Native American, Hispanic, and Asian, in decreasing order of relative risk)

Symptoms and Signs

Primary coccidioidomycosis: Most patients are asymptomatic, but nonspecific respiratory symptoms resembling those of influenza, acute bronchitis, or, less often, acute pneumonia or pleural effusion sometimes occur. Symptoms, in decreasing order of frequency, include fever, cough, chest pain, chills, sputum production, sore throat, and hemoptysis.

Physical signs may be absent or limited to scattered rales with or without areas of dullness to percussion over lung fields. Some patients develop hypersensitivity to the localized respiratory infection, manifested by arthritis, conjunctivitis, erythema nodosum, or erythema multiforme.

Primary pulmonary lesions sometimes leave nodular coin lesions that must be distinguished from tumors, TB, and other granulomatous infections. Sometimes residual cavitary lesions develop; they may vary in size over time and often appear thin-walled. A small percentage of these cavities fail to close spontaneously. Hemoptysis or the threat of rupture into the pleural space occasionally necessitates surgery.

Progressive coccidioidomycosis: Nonspecific symptoms develop a few weeks, months, or occasionally years after primary infection; they include low-grade fever, anorexia, weight loss, and weakness.

Extensive pulmonary involvement may cause progressive cyanosis, dyspnea, and mucopurulent or bloody sputum. Symptoms of extrapulmonary lesions depend on the site. Draining sinus tracts sometimes connect deeper lesions to the skin. Localized extrapulmonary lesions often become chronic and recur frequently, sometimes long after completion of seemingly successful antifungal therapy.

Untreated disseminated coccidioidomycosis is usually fatal and, if meningitis is present, is uniformly fatal without prolonged and possibly lifelong treatment. Mortality rates in patients with advanced HIV infection exceed 70% within 1 mo of diagnosis; whether treatment can alter mortality rates is unclear.

Diagnosis

• Cultures (routine or fungal)

• Microscopic examination of specimens to check for *C. immitis* spherules

• Serologic testing

Eosinophilia may be an important clue in identifying coccidioidomycosis. The diagnosis is suspected based on history and typical physical findings, when apparent; chest x-ray findings can help confirm the diagnosis, which can be established by fungal culture or by visualization of *C. immitis* spherules in sputum, pleural fluid, CSF, exudate from draining lesions, or biopsy specimens. Intact spherules are usually 20 to 80 μm in diameter, thick-walled, and filled with small (2 to 4 μm) endospores. Endospores released into tissues from ruptured spherules may be mistaken for nonbudding yeasts.

Serologic testing for anticoccidioidal antibodies using an immunodiffusion kit (for IgG and IgM antibodies) and complement fixation (for IgG antibodies) are the most useful tests. Titers ≥ 1:4 in serum are consistent with current or recent infection, and higher titers (≥ 1:32) signify an increased likelihood of extrapulmonary dissemination. However, immunocompromised patients may have low titers. Titers should decline during successful therapy. The presence of complement-fixing antibodies in CSF is diagnostic of coccidioidal meningitis and is important because CSF cultures are rarely positive.

Delayed cutaneous hypersensitivity to coccidioidin or spherulin usually develops within 10 to 21 days after acute infections in immunocompetent patients but is characteristically absent in progressive disease. Because this test is positive in most people in endemic areas, its primary value is for epidemiologic studies rather than for diagnosis.

Treatment

• Usually antifungal drugs

Treatment for primary coccidioidomycosis is controversial in low-risk patients. Some experts give fluconazole because its toxicity is low and there is a small risk of hematogenous seeding, especially to bone or brain. In addition, symptoms resolve more quickly in treated patients than in those who are not treated with an antifungal. Others think that fluconazole may blunt the immune response and that risk of hematogenous seeding in primary infection is too low to warrant use of fluconazole. High complement fixation titers indicate spread and the need for treatment.

Mild to moderate nonmeningeal extrapulmonary involvement should be treated with fluconazole ≥ 400 mg po once/day or voriconazole 200 mg po or IV bid. For severe illness, amphotericin B 0.5 to 1.0 mg/kg IV over 2 to 6 h once/day is given for 4 to 12 wk until total dose reaches 1 to 3 g, depending on degree of infection. Patients can usually be switched to an oral azole once they have been stabilized, usually within several weeks.

Patients with HIV- or AIDS-associated coccidioidomycosis require maintenance therapy to prevent relapse; fluconazole 200 mg po once/day or itraconazole 200 mg po bid usually is sufficient, and weekly IV amphotericin B may suffice for azole-intolerant patients. Lipid formulations of amphotericin B are preferred over conventional amphotericin B.

For meningeal coccidioidomycosis, fluconazole is used. The optimal dose is unclear; oral doses of 800 to 1200 mg once/day may be more effective than 400 mg/day. If amphotericin B is used, intrathecal injections are needed, either intraventricularly via a subcutaneous reservoir or intracisternally. Treatment for meningeal coccidioidomycosis must be continued for many months, probably lifelong. Surgical removal of involved bone may be necessary to cure osteomyelitis.

Cryptococcosis

(European Blastomycosis; Torulosis)

Cryptococcosis is a pulmonary or disseminated infection acquired by inhalation of soil contaminated with the encapsulated yeast *Cryptococcus neoformans*. Symptoms are those of pneumonia, meningitis, or involvement of skin, bones, or viscera. Diagnosis is clinical and microscopic, confirmed by culture or fixed-tissue staining. Treatment, when necessary, is with azoles or amphotericin B, with or without flucytosine.

Distribution is worldwide. Cryptococcosis is a defining opportunistic infection for AIDS, although patients with Hodgkin lymphoma, other lymphomas, or sarcoidosis and those taking long-term corticosteroid therapy are also at increased risk.

Pathophysiology

Cryptococcosis is acquired by inhalation and thus typically affects the lungs. Many patients present with

asymptomatic, self-limited primary lung lesions. In immunocompetent patients, the isolated pulmonary lesions usually heal spontaneously without disseminating, even without antifungal therapy.

After inhalation, *Cryptococcus* may disseminate, frequently to the brain and meninges, typically manifesting as microscopic multifocal intracerebral lesions. Meningeal granulomas and larger focal brain lesions may be evident. Although pulmonary involvement is rarely dangerous, meningitis is life-threatening and requires aggressive therapy.

Focal sites of dissemination may also occur in skin, the ends of long bones, joints, liver, spleen, kidneys, prostate, and other tissues. Except for those in the skin, these lesions usually cause few or no symptoms. Rarely, pyelonephritis occurs with renal papillary necrosis.

Involved tissues typically contain cystic masses of yeasts that appear gelatinous because of accumulated cryptococcal capsular polysaccharide, but acute inflammatory changes are minimal or absent.

Symptoms and Signs

Manifestations depend on the affected area.

CNS: Because inflammation is not extensive, fever is usually low grade or absent, and meningismus is uncommon. In patients with AIDS, cryptococcal meningitis may cause minimal or no symptoms, but headache frequently occurs. Because most symptoms of cryptococcal meningitis result from cerebral edema, they are usually nonspecific (eg, headache, blurred vision, confusion, depression, agitation, other behavioral changes). Except for ocular or facial palsies, focal signs are rare until relatively late in the course. Blindness may develop because of cerebral edema or direct involvement of the optic tracts.

Lungs: Many patients are asymptomatic. Those with pneumonia usually have cough and other nonspecific respiratory symptoms. However, AIDS-associated cryptococcal pulmonary infection may manifest as severe, progressive pneumonia with acute dyspnea and an x-ray pattern suggesting *Pneumocystis* infection.

Skin: Dermatologic spread can manifest as pustular, papular, nodular, or ulcerated lesions, which sometimes resemble acne, molluscum contagiosum, or basal cell carcinoma.

Diagnosis

• Culture of CSF, sputum, urine, and blood

• Fixed-tissue specimen staining

Clinical diagnosis is suggested by symptoms of an indolent infection in immunocompetent patients and a more severe, progressive infection in immunocompromised patients. Chest x-ray, urine collection, and lumbar puncture are done first.

Culture of *C. neoformans* is definitive. CSF, sputum, and urine yield organisms most often, and blood cultures may be positive, particularly in patients with AIDS. In disseminated cryptococcosis with meningitis, *C. neoformans* is frequently cultured from urine (prostatic foci of infection sometimes persist despite successful clearance of organisms from the CNS). Diagnosis is strongly suggested if experienced observers identify encapsulated budding yeasts in smears of body fluids, secretions, exudates, or other specimens. In fixed tissue specimens, encapsulated yeasts may also be identified and confirmed as *C. neoformans* by positive mucicarmine or Masson-Fontana staining.

Elevated CSF protein and a mononuclear cell pleocytosis are usual in cryptococcal meningitis, although neutrophilia occasionally predominates. Glucose is frequently low, and encapsulated yeasts forming narrow-based buds can be seen on India ink smears in most patients, especially in those who have AIDS and who typically have a higher fungal burden than those without HIV infection. In some patients with AIDS, CSF parameters are normal, except for the presence of numerous yeasts on India ink preparation. The latex test for cryptococcal capsular antigen is positive in CSF or blood specimens or both in > 90% of

patients with meningitis and is generally specific, although false-positive results may occur, usually with titers ≤ 1:8, especially if rheumatoid factor is also present.

Treatment

• Usually antifungal drugs

Patients without AIDS: Patients may need no treatment for localized pulmonary involvement, confirmed by normal CSF parameters, negative cultures of CSF and urine, and no evidence of cutaneous, bone, or other extrapulmonary lesions. Some experts give a course of fluconazole to prevent hematogenous dissemination and to shorten the course of the illness.

In patients without meningitis, localized lesions in skin, bone, or other sites require systemic antifungal therapy, typically fluconazole 400 mg po once/day for 3 to 6 mo. For more severe disease, amphotericin B 0.5 to 1.0 mg/kg IV once/day with flucytosine 25 mg/kg po q 6 h is given for several weeks.

For meningitis, the standard regimen is amphotericin B 0.7 to 1.0 mg/kg IV once/day plus flucytosine 25 mg/kg po q 6 h for 6 to 10 wk; alternatively, this regimen can be used for 2 wk, followed by fluconazole 400 mg po once/day for 10 wk. After these regimens, patients with AIDS are given fluconazole 200 mg po once/day until the CD4 count is > 200 for at least 6 mo.

Cryptococcal antigen titers should be monitored at the start and end of therapy. However, if the patient is not improving with antifungal drugs, titers should be rechecked while the patient continues to receive therapy; the titers should steadily decline during successful therapy. In general, cultures should become and remain negative for at least 2 wk before treatment is ended.

Patients with AIDS: All patients require treatment. In isolated pulmonary or urinary tract disease, fluconazole 400 mg po once/day is given. For more severe disease, fluconazole 400 mg po once/day plus flucytosine 25 mg/kg po qid is used for 10 wk. For meningitis, the standard regimen is amphotericin B 0.7 to 1.0 mg/kg IV once/day plus flucytosine 25 mg po q 6 h for the first 2 wk of treatment; the entire induction phase of therapy lasts 6 to 10 wk. Alternatively, this regimen can be used for 2 wk, followed by fluconazole 400 mg po once/day for 10 wk total. Once induction therapy is completed, long-term suppressive (maintenance) therapy is required.

Nearly all AIDS patients need maintenance therapy for life. Fluconazole 200 mg po once/day is preferred, but itraconazole at the same dose is acceptable; however, itraconazole serum levels should be measured to make sure that patients are absorbing the drug. Weekly doses of IV amphotericin B also can be used, but this regimen has mostly been replaced by one of the azoles.

Histoplasmosis

Histoplasmosis is a pulmonary and hematogenous disease caused by *Histoplasma capsulatum*; it is often chronic and usually follows an asymptomatic primary infection. Symptoms are those of pneumonia or of nonspecific chronic illness. Diagnosis is by chest x-ray, identification of the organism in sputum or tissue, or both. Treatment, when necessary, is with amphotericin B or an azole.

Histoplasmosis occurs worldwide.

In the US, the endemic area for histoplasmosis includes

• The Ohio-Mississippi River valleys extending into parts of northern Maryland, southern Pennsylvania, central New York, and Texas

Microfoci have been noted in other states, such as Florida.

H. capsulatum grows as a mold in nature or in culture at room temperature but converts to a small (1 to 5 μm in diameter) yeast cell at 37° C and during invasion of host cells. Infection follows inhalation of conidia

(spores produced by the mycelial form of the fungus) in soil or dust contaminated with bird or bat droppings. Severe disease is more common after heavy, prolonged exposure and in men, infants, or people with compromised T-cell-mediated immunity.

Initial infection occurs in the lungs and usually remains there but may spread hematogenously to other organs if it is not controlled by normal cell-mediated host defenses. Progressive disseminated histoplasmosis is one of the defining opportunistic infections for AIDS.

Symptoms and Signs

Most histoplasmosis infections are asymptomatic or so mild that patients do not seek medical attention. The disease has 3 main forms.

Acute primary histoplasmosis is a syndrome with fever, cough, myalgias, chest pain, and malaise of varying severity. Acute pneumonia (evident on physical examination and chest x-ray) sometimes develops.

Chronic cavitary histoplasmosis is characterized by pulmonary lesions that are often apical and resemble cavitary TB. Manifestations are worsening cough and dyspnea, progressing eventually to disabling respiratory dysfunction. Dissemination does not occur.

Progressive disseminated histoplasmosis characteristically includes generalized involvement of the reticuloendothelial system, with hepatosplenomegaly, lymphadenopathy, bone marrow involvement, and sometimes oral or GI ulcerations. The course is usually subacute or chronic, with only nonspecific, often subtle symptoms (eg, fever, fatigue, weight loss, weakness, malaise); the condition of HIV-positive patients may inexplicably worsen. The CNS may become involved, causing meningitis or focal brain lesions. Adrenal infection is rare but may result in Addison's disease. Severe pneumonia is rare, but patients with AIDS may develop severe acute pneumonia with hypoxia suggesting *Pneumocystis jirovecii* infection, as well as hypotension, mental status changes, coagulopathy, or rhabdomyolysis.

Fibrosing mediastinitis, a chronic but rare form, ultimately causes circulatory compromise.

Patients with histoplasmosis may lose vision, but organisms are not present in ocular lesions, antifungal chemotherapy is not helpful, and the link to *H. capsulatum* infection is unclear.

Diagnosis

• Histopathology and cultures

• Antigen testing

The index of suspicion must be high because symptoms are nonspecific. Chest x-rays should be done and may show the following:

• **In acute infection:** Normal or a diffuse nodular or miliary pattern

• **In chronic pulmonary histoplasmosis:** Cavitary lesions in most patients

• **In progressive disease:** Hilar adenopathy with diffuse nodular infiltrates in about 50% of patients

Bronchiolavage or tissue biopsy may be necessary to obtain histology specimens; serologic testing and culture of urine, blood, and sputum specimens are also done.

Microscopic histopathology can strongly suggest the diagnosis, particularly in patients with AIDS and extensive infections; in such patients, intracellular yeasts may be seen in Wright's- or Giemsa-stained peripheral blood or buffy coat specimens. Fungal culture confirms the diagnosis. Lysis-centrifugation or culture of buffy coat improves the yield from blood specimens.

A test for *H. capsulatum* antigen is sensitive and specific, particularly when simultaneous serum and urine

specimens are tested; however, cross-reactivity with other fungi (*Coccidioides immitis, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Penicillium marneffei*) has been noted.

Prognosis

The acute primary form is almost always self-limited, although very rarely, death occurs after massive infection. Chronic cavitary histoplasmosis can cause death due to severe respiratory insufficiency. Untreated progressive disseminated histoplasmosis has a mortality rate of > 90%.

Treatment

• Sometimes no treatment

• Sometimes azole antifungal drugs

• Amphotericin B for serious illness

Acute primary histoplasmosis requires no antifungal therapy unless there is no spontaneous improvement after 1 mo; itraconazole 200 mg po once/day for 6 to 12 wk is then used. Fluconazole and other azoles are also effective. Severe pneumonia requires more aggressive therapy with amphotericin B.

For chronic cavitary histoplasmosis, itraconazole 200 mg po once/day or bid is given for 12 to 24 mo. Other azoles or amphotericin B is used if patients are seriously ill or do not respond to or tolerate itraconazole.

For severe disseminated histoplasmosis, amphotericin B 0.5 to 1.0 mg/kg IV once/day for 4 to 12 wk is the treatment of choice. Patients without AIDS can be switched to itraconazole 200 mg po once/day after they become afebrile and require no ventilatory or BP support. For mild disseminated disease, itraconazole 200 mg po once/day or bid for 9 mo can be used. In patients with AIDS, itraconazole is given indefinitely to prevent relapse. Fluconazole may be less effective, but voriconazole and posaconazole are very active against *H. capsulatum* and may be very effective in the treatment of patients with histoplasmosis. Further data and experience are required to determine which drug is the best in each clinical situation. Intermittent doses of IV amphotericin B can be used for chronic suppression in azole-intolerant patients with AIDS.

Mucormycosis

(Zygomycosis)

Mucormycosis refers to infection caused by diverse fungal species, including *Rhizopus, Rhizomucor, Absidia*, and *Mucor*. Symptoms most frequently result from invasive necrotic lesions in the nose and palate, causing pain, fever, orbital cellulitis, proptosis, and purulent nasal discharge. CNS symptoms may follow. Pulmonary symptoms are severe and include productive cough, high fever, and dyspnea. Diagnosis is primarily clinical, requires a high index of suspicion, and is confirmed by histopathology and culture. Treatment is with IV amphotericin B and surgery to remove necrotic tissue.

Infection is most common among immunocompromised people, in patients with poorly controlled diabetes, and in patients receiving the iron-chelating drug deferoxamine.

The most common form of mucormycosis is

• Rhinocerebral

However, primary cutaneous, pulmonary, or GI lesions sometimes develop, and hematogenous dissemination to other sites can occur.

Symptoms and Signs

Rhinocerebral infections are usually severe and frequently fatal unless diagnosed early and treated aggressively. Necrotic lesions appear on the nasal mucosa or sometimes the palate. Vascular invasion by hyphae leads to progressive tissue necrosis that may involve the nasal septum, palate, and bones surrounding the orbit or sinuses. Manifestations may include pain, fever, orbital cellulitis, proptosis, purulent nasal discharge, and mucosal necrosis.

Progressive extension of necrosis to the brain can cause signs of cavernous sinus thrombosis, seizures, aphasia, or hemiplegia. Pulmonary infections resemble invasive aspergillosis. Pulmonary symptoms (eg, productive cough, high fever, dyspnea) are severe. Cutaneous *Rhizopus* infections have developed under occlusive dressings but more often result from trauma when the injured areas are contaminated with soil.

Diagnosis

• Examination of tissue samples for nonseptate hyphae

Diagnosis requires a high index of suspicion and painstaking examination of tissue samples for large nonseptate hyphae with irregular diameters and right-angle branching patterns; the examination must be thorough because much of the necrotic debris contains no organisms. For unclear reasons, cultures may be negative, even when hyphae are clearly visible in tissues. CT and x-rays often underestimate or miss significant bone destruction.

Treatment

• Control of underlying condition

• Amphotericin B

• Surgical debridement

Effective therapy requires that diabetes be controlled or, if at all possible, immunosuppression be reversed or deferoxamine be stopped.

IV amphotericin B must be used because azoles are ineffective, although recent evidence suggests that posaconazole with or without an echinocandin may be effective. Most experts use high doses of lipid formulations of amphotericin B (up to 10 to 20 mg/kg/day).

Complete surgical debridement of necrotic tissue is critical.

Mycetoma

(Maduromycosis; Madura Foot)

Mycetoma is a chronic, progressive local infection caused by fungi or bacteria and involving the feet, upper extremities, or back. Symptoms include tumefaction and formation of sinus tracts. Diagnosis is clinical, confirmed by microscopic examination of exudates and culture. Treatment includes antimicrobials, surgical debridement, and sometimes amputation.

Bacteria, primarily *Nocardia* sp and other actinomycetes, cause > one half of the cases. The remainder are caused by about 20 different fungal species. When caused by fungi, the lesions are sometimes called eumycetoma.

Mycetoma occurs mainly in tropical or subtropical areas, including the southern US, and is acquired when organisms enter through sites of local trauma on bare skin of the feet or on the extremities or backs of workers carrying contaminated vegetation or other objects. Men aged 20 to 40 are most often affected, presumably because of trauma incurred while working outdoors.

Infections spread through contiguous subcutaneous areas, resulting in tumefaction and formation of

multiple draining sinuses that exude characteristic grains of clumped organisms. Microscopic tissue reactions may be primarily suppurative or granulomatous depending on the specific causative agent. As the infection progresses, bacterial superinfections can develop.

Symptoms and Signs

The initial lesion may be a papule, a fixed subcutaneous nodule, a vesicle with an indurated base, or a subcutaneous abscess that ruptures to form a fistula to the skin surface. Fibrosis is common in and around early lesions. Tenderness is minimal or absent unless acute suppurative bacterial superinfection is present.

Infection progresses slowly over months or years, gradually extending to and destroying contiguous muscles, tendons, fascia, and bones. Neither systemic dissemination nor symptoms and signs suggesting generalized infection occur. Eventually, muscle wasting, deformity, and tissue destruction prevent use of affected limbs. In advanced infections, involved extremities appear grotesquely swollen, forming a club-shaped mass of cystic areas. The multiple draining and intercommunicating sinus tracts and fistulas in these areas discharge thick or serosanguineous exudates containing characteristic grains.

Diagnosis

• Examination and culture of exudates

Causative agents can be identified presumptively by gross and microscopic examination of grains from exudates, which contain irregularly shaped, variably colored, 0.5- to 2- mm granules. Crushing and culture of these granules provides definitive identification. Exudate specimens may yield multiple bacteria and fungi, some of which are potential causes of superinfections.

Treatment

• Antibacterial or antifungal drugs

• Sometimes surgery

Treatment may be required for > 10 yr. Death may result from bacterial superinfection and sepsis if treatment is neglected.

In infections caused by *Nocardia* (see p.), sulfonamides and certain other antibacterial drugs, sometimes in combination, are used.

In infections caused by fungi, certain potential causative organisms may be at least partially sensitive to amphotericin B, itraconazole, or ketoconazole, but many are resistant to all antifungal drugs. Relapses occur after antifungal therapy in most patients, and many patients do not improve or worsen during treatment.

Surgical debridement is necessary, and limb amputation may be needed to prevent potentially fatal severe secondary bacterial infections.

Paracoccidioidomycosis

(South American Blastomycosis)

Paracoccidioidomycosis is progressive mycosis of the lungs, skin, mucous membranes, lymph nodes, and internal organs caused by *Paracoccidioides brasiliensis*. Symptoms are skin ulcers, adenitis, and pain due to abdominal organ involvement. Diagnosis is clinical and microscopic, confirmed by culture. Treatment is with azoles (eg, itraconazole), amphotericin B, or sulfonamides.

Infections occur only in discrete foci in South and Central America, most often in men aged 20 to 50,

especially coffee growers of Colombia, Venezuela, and Brazil. Although a relatively unusual opportunistic infection, paracoccidioidomycosis sometimes occurs in immunocompromised patients, including those with AIDS. Although specific natural sites for *Paracoccidioides brasiliensis* remain undefined, it is presumed to exist in soil as a mold, with infection due to inhalation of conidia (spores produced by the mycelial form of the fungus). Conidia convert to invasive yeasts in the lungs and are assumed to spread to other sites via blood and lymphatics.

Symptoms and Signs

Most people who inhale conidia of *P. brasiliensis* do not become ill; illness, if it occurs, usually manifests as acute pneumonia, which may spontaneously resolve. Clinically apparent infections can become chronic and progressive but are not usually fatal. There are 3 patterns:

- **Mucocutaneous:** Infections most often involve the face, especially at the nasal and oral mucocutaneous borders. Yeasts are usually abundantly present within pinpoint lesions throughout granular bases of slowly expanding ulcers. Regional lymph nodes enlarge, become necrotic, and discharge necrotic material through the skin.

- **Lymphatic:** Cervical, supraclavicular, or axillary nodes enlarge but are painless.

- **Visceral:** Typically, focal lesions cause enlargement mainly of the liver, spleen, and abdominal lymph nodes, sometimes causing abdominal pain.

Infections may be mixed, involving combinations of all 3 patterns.

Diagnosis

Clinical findings suggest the diagnosis. Culture is diagnostic, although observation of large (often > 15 μm) yeasts that form characteristic multiple buds (pilot wheel) in specimens provides strong presumptive evidence.

Treatment

- Antifungal drugs

Azoles are highly effective. Oral itraconazole is generally considered the drug of choice, primarily because it costs less than other azoles that are available in endemic areas. IV amphotericin B can also eliminate the infection and is often used in very severe cases. Sulfonamides, which are widely used in some countries because they are inexpensive, can suppress growth and cause lesions to regress but are not curative.

Pigmented Fungi

(Chromoblastomycosis; Chromomycosis; Phaeohyphomycosis; Verrucous Dermatitis)

Chromoblastomycosis is a cutaneous infection caused by dematiaceous (pigmented) fungi. Symptoms are ulcerating nodules on exposed body parts; extracutaneous infections (termed phaeohyphomycosis) in subcutaneous tissues, sinuses, the brain, and other tissues may occur. Diagnosis is by appearance, histopathology, and culture. Treatment is with itraconazole, another azole, or flucytosine and surgical excision.

Chromoblastomycosis is a cutaneous infection affecting normal, immunocompetent people mostly in tropical or subtropical areas; it is characterized by formation of papillomatous nodules that tend to ulcerate. Pigmented fungi have been increasingly recognized as opportunists affecting immunosuppressed patients. These infections are caused by many kinds of dark, melanin-pigmented dematiaceous fungi including species of *Bipolaris, Cladophialophora, Cladosporium, Drechslera, Exophiala, Fonsecaea, Phialophora, Xylohypha, Ochronosis, Rhinocladiella, Scolecobasidium*, and *Wangiella*.

Symptoms and Signs

Most infections begin on the foot or leg, but other exposed body parts may be infected, especially where the skin is broken. Early small, itchy, enlarging papules may resemble dermatophytosis (ringworm). These papules extend to form dull red or violaceous, sharply demarcated patches with indurated bases. Several weeks or months later, new lesions, projecting 1 to 2 mm above the skin, may appear along paths of lymphatic drainage. Hard, dull red or grayish cauliflower-shaped nodular projections may develop in the center of patches and gradually extend to cover extremities for up to 4 to 15 yr. Lymphatics may be obstructed, itching may persist, and secondary bacterial superinfections may develop, causing ulcerations and occasionally septicemia.

Extracutaneous infections (phaeohyphomycosis) may occur. They include invasive sinusitis, sometimes with bone necrosis, as well as subcutaneous nodules or abscesses, keratitis, lung masses, osteomyelitis, mycotic arthritis, intramuscular abscess, endocarditis, brain abscess, and chronic meningitis.

Dematiaceous fungi only rarely cause fatal infections in patients who have normal, intact host defense mechanisms. Life-threatening illnesses occur more often in immunocompromised patients.

Diagnosis

• Culture

• Sometimes tissue staining

Late chromoblastomycosis lesions have a characteristic appearance, but early lesions may be mistaken for dermatophytoses. Phaeohyphomycosis must be distinguished from myriad other infectious and noninfectious conditions by histopathology and culture.

Dematiaceous fungi are frequently discernible in tissue specimens stained with conventional hematoxylin and eosin; they appear as septate, brownish bodies, reflecting their natural melanin content. Fontana-Masson staining for melanin confirms their presence. Culture is needed to identify the causative species.

Treatment

• Itraconazole, sometimes with flucytosine

• Often surgery

Itraconazole is the most effective drug, although not all patients respond. Flucytosine is sometimes added to prevent relapse. Fluconazole seldom causes lesions to regress, and amphotericin B is ineffective. The role of voriconazole and posaconazole has not yet been determined.

Many cases require surgical excision for cure.

Sporotrichosis

Sporotrichosis is a cutaneous infection caused by the saprophytic mold *Sporothrix schenckii*. Pulmonary and hematogenous involvement is uncommon. Symptoms are cutaneous nodules that spread via lymphatics and break down into abscesses and ulcers. Diagnosis is by culture. Treatment is with itraconazole or amphotericin B.

Sporothrix schenckii resides on rose or barberry bushes, in sphagnum moss, and in other mulches. Horticulturists, gardeners, farm laborers, and timber workers are most often infected, typically after minor trauma involving contaminated material. In contrast to the other dimorphic fungi, *S. schenckii* is not usually inhaled but enters the body through small cuts and abrasions in the skin.

Symptoms and Signs

Lymphocutaneous infections are most common. They characteristically involve one hand and arm, although they can occur anywhere on the body; primary lesions may occur on exposed surfaces of the feet or face.

A primary lesion may appear as a small, nontender papule or, occasionally, as a slowly expanding subcutaneous nodule that eventually becomes necrotic and sometimes ulcerates. Typically, a few days or weeks later, a chain of draining lymph nodes begins to enlarge slowly but progressively, forming movable subcutaneous nodules. Without treatment, overlying skin reddens and may later necrose, sometimes causing an abscess, ulceration, and bacterial superinfection. Systemic symptoms and signs of infection are notably absent.

Lymphocutaneous sporotrichosis is chronic and indolent; it is potentially fatal only if bacterial superinfections cause sepsis.

Rarely, in patients without primary lymphocutaneous lesions, hematogenous spread leads to indolent infections of multiple peripheral joints, sometimes bones, and, less often, genitals, liver, spleen, kidneys, or meninges. Equally rare is chronic pneumonia caused by inhaling spores and manifested by localized infiltrates or cavities, most often in patients with preexisting chronic lung disease.

Diagnosis

• Culture

The illness must be differentiated from local infections caused by *Mycobacterium tuberculosis*, atypical mycobacteria, *Nocardia*, or other organisms. During the early, nondisseminated stage, the primary lesion is sometimes misdiagnosed as a spider bite. Culture of tissue from the active infection site provides the definitive diagnosis. *S. schenckii* yeasts can be seen only rarely in fixed-tissue specimens, even with special staining. Serologic tests are not available.

Treatment

• Itraconazole

Oral itraconazole, given for 3 to 6 mo, is the treatment of choice. Severe infection and infection in patients with AIDS require IV amphotericin B. AIDS patients may require lifelong maintenance therapy with itraconazole. Voriconazole and posaconazole may have a role.

Miscellaneous Opportunistic Fungi

Many yeasts and molds can cause opportunistic, even life-threatening infections in immunocompromised patients. These infections only rarely affect immunocompetent people. Yeasts tend to cause fungemia as well as focal involvement of skin and other sites.

Trichosporon beigelii (most now known as *T. asahii*) and *Blastoschizomyces capitatus* particularly affect neutropenic patients.

Malassezia furfur fungemia typically affects infants and debilitated adults receiving lipid-containing IV hyperalimentation infusions.

Penicillium marneffei was recognized as an opportunistic invader in Southeast Asian patients with AIDS, and cases have been recognized in the US. *P. marneffei* skin lesions may resemble molluscum contagiosum.

Especially in neutropenic patients, various environmental molds, including species of *Fusarium* and *Scedosporium*, both of which are becoming more frequent, can cause focal vasculitic lesions mimicking invasive aspergillosis.

Specific diagnosis requires culture and species identification and is crucial because not all of these organisms respond to any single antifungal drug. For example, *Scedosporium* sp are typically resistant to amphotericin B. Optimal regimens of antifungal therapy for each member of this group of fungal opportunists must be defined.

Chapter 143. Approach to Parasitic Infections

Introduction

Parasitic infections are responsible for substantial morbidity and mortality worldwide. They are prevalent in Central and South America, Africa, and Asia. They are much less common in Australia, Canada, Europe, Japan, New Zealand, and the US. By far, the greatest impact is on residents of developing areas, but parasitic infections are encountered in developed countries among immigrants and travelers returning from endemic regions and, on occasion, even among residents who have not traveled, particularly those with AIDS or other causes of immunodeficiency.

Many parasitic infections are spread through fecal contamination of food or water. They are most frequent in impoverished areas where sanitation and hygiene are poor. Some parasites, such as the hookworm, can enter the skin during contact with infected dirt or, in the case of schistosomes, with freshwater. Others, such as malaria, are transmitted by arthropod vectors. Rarely, parasites are transmitted via blood transfusions or shared needles or congenitally from mother to fetus.

Some parasites are endemic in the US and other developed countries. Examples are the pinworm, *Enterobius vermicularis, Trichomonas vaginalis*, toxoplasmosis, and enteric parasites such as *Giardia intestinalis (lamblia)* and *Cryptosporidium* spp.

Taxonomically, parasites can be divided into 2 major groups:

• Protozoa

• Helminths (worms)

The characteristics of protozoan and helminthic infections vary in important ways.

Protozoa: Protozoa are single-celled organisms that multiply by simple binary division (see Chs. 147 and 148). Protozoa can multiply in their human hosts, increasing in number to cause overwhelming infection. With rare exceptions, protozoan infections do not cause eosinophilia.

Helminths: Helminths are multicellular and have complex organ systems. Helminths can be further divided into

• Roundworms (nematodes—see Ch. 144)

• Flatworms (platyhelminthes), which include tapeworms (cestodes—see Ch. 146)

• Flukes (trematodes—see Ch. 145)

Some parasites have adapted to living in the lumen of the intestine where conditions are anaerobic; others reside in blood or tissues in aerobic conditions.

In contrast to protozoa, helminths do not multiply in humans but can elicit eosinophilic responses when they migrate through tissue. Most helminths have complex life cycles that involve substantial time outside their human hosts. Exceptions are *Strongyloides stercoralis, Capillaria philippinensis*, and *Hymenolepis nana*, which can increase in number because of autoinfection. In strongyloidiasis, autoinfection can result in life-threatening, disseminated hyperinfections in immunosuppressed people, particularly those taking corticosteroids.

The severity of helminthic infections usually correlates with the worm burden, but there are exceptions as when a single ascaris causes life-threatening pancreatitis by migrating into the pancreatic duct. The worm burden depends on the degree of environmental exposure, parasite factors, and the host's genetically determined immune responses. If a person moves from an endemic area, the number of adult worms diminishes over time. Although a few parasites (eg, *Clonorchis sinensis*) can survive for decades, many

species have life spans of only a few years or less. More information about parasitic infections is available at the CDC's Division of Parasitic Diseases.

Diagnosis

Methods for the diagnosis of specific parasitic infections are discussed in the chapters to follow and are summarized in
Table 143-1.

Parasitic infections should be considered in the differential diagnosis of clinical syndromes in residents of or travelers to areas where sanitation and hygiene are poor or where vector-borne diseases are endemic. For example, fever in the returning traveler suggests the possibility of malaria. Experience indicates that immigrants from developing areas to developed countries who return home to visit friends and relatives are at particular risk. They frequently do not seek or cannot afford pretravel advice on disease prevention and are more likely to enter high-risk settings than tourists who stay at resort facilities. Although less frequent, the possibility of an endemic or imported parasitic infection must also be considered in residents of developed countries who present with suggestive

[**Table 143-1.** Collecting and Handling Specimens for Microscopic Diagnosis of Parasitic Infections]

clinical syndromes, even if they have not traveled.

Historical information, physical findings, and laboratory data may also suggest specific parasitic infections. For example, eosinophilia is common when helminths migrate through tissue and suggests a parasitic infection in an immigrant or returning traveler.

Physicians with expertise in parasitic infections and tropical medicine are available for consultation at many major medical centers, travel clinics, and public health facilities.

"Laboratory Identification of Parasites of Public Health Concern" provides detailed descriptions of diagnostic methods and is available from the Centers for Disease Control and Prevention (CDC) at www.dpd.cdc.gov/dpdx.

GI tract parasites: Various stages of protozoa and helminths that infect the GI tract are typically shed in the stool. Routine detection requires examination of stool specimens, preferably 3 collected on different days, because shedding can be sporadic. With some parasites, relatively sensitive and specific assays are available to detect antigens in stool.

Freshly passed stools uncontaminated with urine, water, dirt, or disinfectants should be sent to the laboratory within 1 h; unformed or watery stools are most likely to contain motile trophozoites. If not examined immediately, stools should be refrigerated, but not frozen. Portions of fresh stools should also be emulsified in fixative to preserve GI protozoa. Concentration techniques can be used to improve sensitivity. Anal cellophane tape or swabs may collect pinworm or tapeworm eggs. If strongyloidiasis is suspected, fresh stool should be smeared on an agar plate and incubated to identify the tracks of migrating larvae. Antibiotics, x-ray contrast material, purgatives, and antacids can hinder detection of ova and parasites for several weeks. Serologic assays, antigen detection tests (eg, for *Giardia intestinalis*, *Cryptosporidium* sp, or *Entamoeba histolytica*), or PCR testing may aid in diagnosis (see Table 143-2). Sensitivity of stool examinations for ova and parasites is low enough that when clinical suspicion is strong, empirical treatment may be given.

Sigmoidoscopy or colonoscopy should be considered when routine stool examinations are negative and amebiasis is suspected in patients with persistent GI symptoms. Sigmoidoscopic specimens should be collected with a curet or spoon (cotton swabs are not suitable) and processed immediately for microscopy. Duodenal aspirates or small-bowel biopsy specimens may be necessary for diagnosis of such infections as cryptosporidiosis and microsporidiosis.

[**Table 143-2.** Serologic and Molecular Tests for Parasitic Infection]

Serologic testing for parasitic infections: Some parasites can be detected by serologic tests (see Table 143-2).

Treatment

Advice for treating parasitic infections is available from experts at major medical and public health centers and travel clinics, in textbooks of infectious diseases and tropical medicine, and in summary form from *The Medical Letter on Drugs and Therapeutics* . Drugs for unusual parasitic infections can be obtained from the manufacturer or from the CDC Drug Service.

Prevention

Despite substantial investment and research, no vaccines are yet available for prevention of human parasitic infections. Prevention is based on avoidance strategies.

Transmission of most intestinal parasites can be prevented by

• Sanitary disposal of feces

• Adequate cooking of food

• Provision of purified water

For the international traveler, the best advice is "cook it, boil it, peel it, or forget it." When followed, these measures substantially reduce the risk of intestinal parasitic infections as well as risk of bacterial and viral gastroenteritis. Meat, particularly pork, and fish, particularly freshwater varieties, should be thoroughly cooked before ingestion. Other safety measures include removing litter boxes from areas where food is prepared to prevent toxoplasmosis. People should not swim in freshwater lakes, streams, or rivers in areas where schistosomiasis is endemic or walk barefoot in areas where hookworms are found.

The risk of malaria and many other vector-borne diseases can be decreased by wearing long-sleeved shirts and pants and applying diethyltoluamide (DEET)-containing insect repellants to exposed skin and permethrin to clothing. Window screens, air-conditioning, and mosquito nets impregnated with permethrin or other insecticides provide further protection. In addition, prophylactic antimalarial drugs should be taken by those traveling in endemic regions.

Travelers to rural Latin America should not sleep in adobe dwellings where reduviid bugs can transmit Chagas disease. In Africa, travelers should avoid bright colors and wear long-sleeved shirts and pants to avoid tsetse flies in regions where African sleeping sickness occurs.

Country-specific recommendations for travel are available from the CDC web site (www.cdc.gov/travel) and in *CDC Health Information for International Travel 2010.*

Chapter 144. Nematodes (Roundworms)

Introduction

Nematodes are nonsegmented cylindric worms ranging from 1 mm to 1 m in length. Nematodes have a body cavity, distinguishing them from tapeworms and flukes. Depending on the species, different stages in the life cycle are infectious to humans. Hundreds of millions of humans are infected with nematodes; the most common are *Ascaris*, hookworms, and *Trichuris*.

Angiostrongyliasis

Angiostrongyliasis is infection with larvae of worms of the genus *Angiostrongylus*; intestinal symptoms or eosinophilic meningitis occurs depending on the infecting species.

Angiostrongylus are parasites of rats. Excreted larvae are taken up by intermediate hosts (snails and slugs) and transport hosts (certain crabs and freshwater shrimp). Human infection is acquired by ingestion of raw or undercooked snails or slugs or transport hosts; it is unclear whether larval contamination of vegetables (eg, in slime from snails or slugs that crawl on the food) can cause infection.

A. cantonensis infection occurs predominantly in Southeast Asia and the Pacific Basin, although infection has been reported elsewhere. The larvae migrate from the GI tract to the meninges, where they cause eosinophilic meningitis, with fever, headache, and meningismus. Occasionally, ocular invasion occurs.

A. costaricensis infection occurs in the Americas. Adult worms reside in arterioles of the ileocecal area, and eggs can be released into the intestinal tissues, resulting in local inflammation with abdominal pain, vomiting, and fever. Abdominal angiostrongyliasis mimics appendicitis; a painful right lower quadrant mass may develop.

Diagnosis is suspected based on a history of ingesting potentially contaminated material. Patients with meningeal findings require lumbar puncture; CSF shows eosinophilia, but parasites are rarely visible. Diagnosis of GI infection is difficult because larvae and eggs are not present in stool; however, if surgery is done (eg, for suspected appendicitis), eggs and larvae can be identified in tissues removed during surgery.

A. cantonensis meningitis is treated with analgesics, corticosteroids, and removal of CSF at frequent intervals to reduce CNS pressure. Most patients have a self-limited course and recover completely.

Treatment of *A. costaricensis* infection is controversial. Anthelmintics do not appear to be effective and may be harmful because of the inflammatory response provoked by antigen released from dead parasites.

Anisakiasis

Anisakiasis is infection with larvae of worms of the genus *Anisakis* and related genera such as *Pseudoterranova*. Infection is acquired by eating raw or poorly cooked saltwater fish; larvae burrow into the mucosa of the GI tract, causing discomfort.

Anisakis is a parasite that resides in the GI tract of marine mammals. Excreted eggs hatch into free-swimming larvae, which are ingested by fish and squid; human infection is acquired by ingestion of these intermediate hosts in a raw or undercooked state. Thus, infection is particularly common in locations and cultures in which raw fish is traditionally consumed. Larvae burrow into the stomach and small bowel.

Symptoms typically include abdominal pain, nausea, and vomiting; intestinal infection may create an inflammatory mass causing symptoms resembling Crohn's disease.

Diagnosis

• Upper endoscopy

Diagnosis is usually made by upper endoscopy; stool examination is unhelpful, but a serologic test is available in some countries. Infection typically resolves spontaneously after several weeks; rarely, it persists for months. Endoscopic removal of the larvae is curative.

Treatment

• Albendazole

Treatment with albendazole 400 mg po as a single dose may be effective. Cooking to > 50° C (> 122° F) or freezing for > 24 h destroys larvae; they may resist pickling, salting, and smoking.

Ascariasis

Ascariasis is infection with *Ascaris lumbricoides*. Light infections may be asymptomatic. Early symptoms are pulmonary (cough, wheezing); later symptoms are GI, with cramps or abdominal pain due to obstruction of GI lumina (intestines or biliary or pancreatic ducts) by adult worms. Chronically infected children may develop undernutrition. Diagnosis is by identifying eggs or adult worms in stool, adult worms that migrate from the nose or mouth, or larvae in sputum during the pulmonary migration phase. Treatment is with albendazole, mebendazole, or pyrantel pamoate.

Pathophysiology

Ingested eggs hatch in the duodenum, and the resulting larvae penetrate the wall of the small bowel and migrate via the portal circulation through the liver to the heart and lungs. Larvae lodge in the alveolar capillaries, penetrate alveolar walls, and ascend the bronchial tree into the oropharynx. They are swallowed and return to the small bowel, where they develop into adult worms, which mate and release eggs into the stool. The life cycle is completed in about 2 to 3 mo; adult worms live 1 to 2 yr.

A tangled mass of worms resulting from heavy infection can obstruct the bowel, particularly in children. Aberrantly migrating individual adult worms occasionally obstruct the biliary or pancreatic ducts, causing cholecystitis or pancreatitis; cholangitis, liver abscess, and peritonitis are less common. Fever due to other illnesses or certain drugs (eg, albendazole, mebendazole, tetrachloroethylene) may trigger aberrant migration.

Etiology

Ascariasis occurs worldwide. It is concentrated in tropical and subtropical areas with poor sanitation, but transmission also occurs in rural areas of the southeastern US. Ascariasis is the most prevalent intestinal helminth infection in the world. Current estimates suggest that > 1.3 billion people are infected, and about 20,000 infected people (mostly children) die each year of bowel or biliary obstruction. An estimated 4 million people in the US are infected.

Symptoms and Signs

Larvae migrating through the lungs may cause cough, wheezing, and occasionally hemoptysis or other respiratory symptoms. Adult worms in small numbers usually do not cause GI symptoms, although passage of an adult worm by mouth or rectum may bring an otherwise asymptomatic patient to medical attention. Bowel or biliary obstruction causes cramping abdominal pain, nausea, and vomiting. Jaundice is uncommon. Even moderate infections can lead to undernutrition in children. The pathophysiology is unclear and may include competition for nutrients, impairment of absorption, and depression of appetite.

Diagnosis

• Microscopic examination of stool

Diagnosis is by microscopic detection of eggs in stools. Occasionally, larvae can be found in sputum during the pulmonary phase.

Eosinophilia can be marked while larvae migrate though the lungs but usually subsides later when adult worms reside in the intestine. Chest x-ray during the pulmonary phase may show infiltrates (Loffler's syndrome).

Treatment

• Albendazole

All infections should be treated. Albendazole 400 mg po once, mebendazole 100 mg po bid for 3 days, or ivermectin 150 to 200 μg/kg once is effective. Albendazole, mebendazole, and ivermectin should not be used during pregnancy. Nitazoxanide is effective for mild *Ascaris* infections but less so for heavy infections. Piperazine, once widely used, has been replaced by less toxic alternatives.

Obstructive complications may respond to anthelmintic therapy or require surgical or endoscopic extraction of adult worms.

Prevention

Prevention requires adequate sanitation. Uncooked or unwashed vegetables should be avoided in areas where human feces are used as fertilizer.

Dracunculiasis

(Guinea Worm Disease; Fiery Serpent)

Dracunculiasis is infection with *Dracunculus medinensis*. Symptoms are a painful, inflamed skin lesion, which contains an adult worm, and debilitating arthritis. Diagnosis is by inspection. Treatment is slow removal of the adult worm.

Twenty years ago, dracunculiasis was endemic in much of tropical Africa, Yemen, India, and Pakistan. Today, because of international efforts to interrupt transmission, infection occurs mainly within a narrow belt of African countries and Yemen.

Pathophysiology

Humans become infected by drinking water containing infected microcrustaceans (copepods). The larvae are released, penetrate the bowel wall, and mature in the abdominal cavity into adult worms in about 1 yr. After mating, the male dies, and the gravid female migrates through subcutaneous tissues, usually to the distal lower extremities. The cephalic end of the worm produces an indurated papule that vesiculates and eventually ulcerates. On contact with water, a loop of the worm's uterus prolapses through the skin and discharges motile larvae. Worms that do not reach the skin die and disintegrate or become calcified. Larvae are ingested by copepods.

In most endemic areas, transmission is seasonal and each infectious episode lasts about 1 yr.

Symptoms and Signs

Infection is initially asymptomatic; symptoms usually develop when the worm erupts. Local symptoms include intense itching and a burning pain at the site of the skin lesion. Urticaria, erythema, dyspnea, vomiting, and pruritus are thought to reflect allergic reactions to worm antigens. If the worm is broken during expulsion or extraction, a severe inflammatory reaction ensues with disabling pain. Symptoms subside and the ulcer heals once the adult worm is expelled. In about 50% of cases, secondary bacterial infections occur along the track of the emerging worm. Chronic sequelae include fibrous ankylosis of joints and contraction of tendons.

Diagnosis

• Clinical evaluation

Diagnosis is obvious once the white, filamentous adult worm appears at the cutaneous ulcer. Calcified worms can be localized with x-ray examination; they have been found in Egyptian mummies. Serodiagnostic tests are not specific.

Treatment

• Manual removal

Treatment consists of slow removal of the adult worm over days to weeks by rolling it on a stick. Surgical removal under local anesthesia is an option but is seldom available in endemic areas. There are no effective drugs for this disease; the beneficial effect of metronidazole (250 mg tid for 10 days) has been ascribed to the drug's anti-inflammatory and antibacterial properties rather than to anthelmintic effects.

Prevention

Filtering drinking water through a piece of cheesecloth, chlorination, or boiling effectively protects against dracunculiasis.

Filarial Nematode Infections

Threadlike adult filarial worms reside in lymphatic or subcutaneous tissues. Gravid females produce live offspring (microfilariae) that circulate in blood or migrate through tissues. When ingested by a suitable bloodsucking insect (mosquitoes or flies), microfilariae develop into infective larvae that are inoculated or deposited in the skin of the next host during the insect bite. Life cycles of all filarial worms are similar except for the site of infection. Only a few filarial species infect humans.

Subcutaneous filariasis is caused by *Loa loa* (the African eye worm) and *Onchocerca volvulus*.

Lymphatic filariasis is caused by *Wuchereria bancrofti, Brugia malayi*, and *B. timori*.

Dirofilariasis

(Dog Heartworm Infection)

***Dirofilaria immitis* is the dog heartworm, which is transmitted to humans by infected mosquitoes.**

Symptomatic human infection is very rare, but larvae may become encapsulated in infarcted lung tissue and produce well-defined pulmonary nodules.

Patients may have chest pain, cough, and occasionally hemoptysis. Many patients remain asymptomatic, and a pulmonary nodule, which may suggest a tumor, is discovered during routine chest x-ray.

Diagnosis is by histologic examination of a surgical specimen. No treatment is indicated in humans; infection is self-limited.

Loiasis

Loiasis is infection with *Loa loa*. Symptoms include localized angioedema (Calabar swellings) and subconjunctival migration of adult worms. Diagnosis is by detecting microfilariae in peripheral blood or seeing worms migrating across the eye. Treatment is with diethylcarbamazine.

Loiasis is confined to the rain forest belt of western and central Africa. Humans are the only known

natural reservoir for this parasite.

Loa loa microfilariae are transmitted by day-biting tabanid flies (*Chrysops* [deerfly or horsefly]). Microfilariae mature to adult worms in the subcutaneous tissues of the human host; females are 40 to 70 mm long, and males are 30 to 34 mm long. The adults produce more microfilariae. Adults migrate in subcutaneous tissues and the eye, and microfilariae circulate in blood. Flies become infected when they ingest blood from a human host during the day (when microfilaremia levels are the highest).

Occasionally, infection causes cardiomyopathy, nephropathy, or encephalitis.

Symptoms and Signs

Infection produces areas of angioedema (Calabar swellings) that develop anywhere on the body but predominantly on the extremities; they are presumed to reflect hypersensitivity reactions to allergens released by migrating adult worms. In native residents, swellings usually last 1 to 3 days but are more frequent and severe in visitors. Worms may also migrate subconjunctivally across the eyes. This migration may be unsettling, but residual eye damage is uncommon.

Nephropathy generally manifests as proteinuria with or without mild hematuria and is believed to be due to immune complex deposition. Encephalopathy is usually mild, with vague CNS symptoms.

Diagnosis

• Microscopic examination of blood samples

Microscopic detection of microfilariae in peripheral blood establishes the diagnosis. Blood samples should be drawn around noontime, when microfilaremia levels are the highest. Serologic tests for antibodies do not differentiate *Loa loa* from other filarial nematode infections.

Treatment

• Diethylcarbamazine

Diethylcarbamazine (DEC) is the only drug that kills microfilariae and adult worms. Patients with microfilariae in the blood are given DEC 50 mg po on day 1, 50 mg po tid on day 2, 100 mg tid on day 3, then 2 mg/kg tid on days 4 through 14. A single dose of 6 mg/kg has been used in mass treatment programs. Multiple courses may be necessary before resolution is complete.

DEC transiently exacerbates proteinuria and, in heavily infected patients, may trigger encephalopathy, leading to coma and death. Such patients may benefit from apheresis or initial treatment with albendazole, and multiple courses of therapy may be necessary. Ivermectin has also been used to reduce microfilaremia, but albendazole is preferred because its onset of action is slower and risk of precipitating encephalopathy is lower.

Prevention

DEC 300 mg po once/wk can be used to prevent infection. Using insect repellents (including permethrin-impregnated clothing) and wearing long-sleeved and long-legged clothing may reduce the number of bites by infected flies. Because the flies are day-biting, mosquito (bed) nets do not help.

Bancroftian and Brugian Lymphatic Filariasis

Lymphatic filariasis is infection with any of 3 species of *Filarioidea*. Acute symptoms include fever, lymphadenitis, lymphangitis, funiculitis, and epididymitis. Chronic symptoms include abscesses, hyperkeratosis, polyarthritis, hydroceles, lymphedema, and elephantiasis. Tropical pulmonary eosinophilia with bronchospasm, fever, and pulmonary infiltrates is another manifestation of infection. Diagnosis is by detection of microfilariae in blood, ultrasound visualization of adult worms, or serologic testing. Treatment is with diethylcarbamazine;

antibiotics are used for complicating bacterial cellulitis.

Etiology

Lymphatic filariasis is caused by *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori*. Transmission is by mosquitoes. Infective larvae from the mosquito migrate to the lymphatics, where they develop into threadlike adult worms within 6 to 12 mo. Females are 80 to 100 mm long; males are about 40 mm long. Gravid adult females produce microfilariae that circulate in blood.

Bancroftian filariasis is present in tropical and subtropical areas of Africa, Asia, the Pacific, and the Americas, including Haiti. Brugian filariasis is endemic in South and Southeast Asia. Current estimates suggest that about 120 million people are infected.

Symptoms and Signs

Infection can result in microfilaremia without overt clinical manifestations. Symptoms and signs are caused primarily by adult worms. Microfilaremia gradually disappears after people leave the endemic area.

Acute inflammatory filariasis consists of 4- to 7-day episodes (often recurrent) of fever and inflammation of lymph nodes with lymphangitis (termed acute adenolymphangitis [ADL]) or acute epididymitis and spermatic cord inflammation. Localized involvement of a limb may cause an abscess that drains externally and leaves a scar. ADL is often associated with secondary bacterial infections. ADL episodes usually precede onset of chronic disease by ≥ 2 decades. Acute filariasis is more severe in previously unexposed immigrants to endemic areas than in native residents.

Chronic filarial disease develops insidiously after many years. In most patients, asymptomatic lymphatic dilation occurs, but chronic inflammatory responses to adult worms and secondary bacterial infections may result in chronic lymphedema of the affected body area or in scrotal hydroceles. Chronic pitting lymphedema of a lower extremity can progress to elephantiasis. Increased local susceptibility to bacterial and fungal infections contributes to the development of elephantiasis. Other forms of chronic filarial disease are caused by disruption of lymphatic vessels or aberrant drainage of lymph fluid, leading to chyluria and chyloceles.

Extralymphatic signs include chronic microscopic hematuria and proteinuria and mild polyarthritis, all presumed to result from immune complex deposition.

Tropical pulmonary eosinophilia (TPE) is an uncommon manifestation with recurrent bronchospasm, transitory lung infiltrates, low-grade fever, and marked eosinophilia. It is most likely due to hypersensitivity reactions to microfilariae. Chronic TPE can lead to pulmonary fibrosis.

Diagnosis

• Microscopic examination of blood samples

Microscopic detection of microfilariae in blood establishes the diagnosis. Filtered or centrifuged concentrates of blood are more sensitive than thick blood films. Blood samples must be obtained when microfilaremia peaks—at night where *W. bancrofti* is endemic, but during the day in many Pacific islands where *B. malayi* and *B. timori* occur. Viable adult worms can be visualized in dilated lymphatics by ultrasonography; their movement has been called the filarial dance.

A rapid-format immunochromatographic antigen test specific for *W. bancrofti* has recently been evaluated in the field. Antibody detection is of limited value; there is substantial antigenic cross-reactivity between filariae and other helminths, and a positive serologic test does not distinguish between past and current infection. PCR-based assays for DNA of *W. bancrofti* and *B. malayi* are available in research settings.

Treatment

• Diethylcarbamazine

Optimal treatment is uncertain. Diethylcarbamazine (DEC) kills microfilariae and a variable proportion of adult worms. The DEC dose in patients with heavy microfilaremia is 50 mg po on day 1, 50 mg tid on day 2, 100 mg tid on day 3, then 2 mg/kg tid on days 4 to 14. A single dose of albendazole (400 mg po) with either ivermectin (200 µg/kg po) or DEC (6 mg/kg) rapidly reduces microfilaremia levels, but ivermectin does not kill adult worms.

Also, doxycycline has been given long-term (eg, 8 wk). Doxycycline kills *Wolbachia* endosymbiont bacteria within filaria, leading to death of the worms.

Acute attacks of ADL usually resolve spontaneously, although antibiotics may be required to control secondary bacterial infections. Whether DEC therapy prevents or lessens chronic lymphedema remains controversial.

Chronic lymphedema requires meticulous skin care, including use of systemic antibiotics to treat secondary bacterial infections; these antibiotics may slow or prevent progression to elephantiasis. Conservative measures such as elastic bandaging of the affected limb reduce swelling. Surgical decompression using nodal-venous shunts to improve lymphatic drainage offers some long-term benefit in extreme cases of elephantiasis. Massive hydroceles can also be managed surgically.

TPE responds to DEC (2 mg/kg tid for 12 to 21 days), but relapses occur in up to 25% of patients and require additional courses of therapy.

Prevention

Avoiding mosquito bites in endemic areas is the best protection (eg, by using diethyltoluamide [DEET], permethrin-impregnated clothing, and bed nets). Chemoprophylaxis with DEC or combinations of antifilarial drugs (ivermectin/albendazole or ivermectin/DEC) can suppress microfilaremia and thereby reduce transmission of the parasite by mosquitoes in endemic communities. DEC has even been used as an additive to table salt in some endemic areas.

Onchocerciasis

(River Blindness)

Onchocerciasis is infection with the filarial nematode *Onchocerca volvulus*. Symptoms are subcutaneous nodules, pruritus, adenopathy, lymphatic obstruction, chronic skin disease, and eye lesions that may lead to blindness. Diagnosis is by finding microfilariae in skin snips, the cornea, or the anterior chamber of the eye; identifying adult worms in subcutaneous nodules; or using PCR or DNA probes. Treatment is with ivermectin.

Pathophysiology

Onchocerciasis is spread by blackflies (*Simulium* sp) that breed in swiftly flowing streams (hence, the term river blindness). Infective larvae inoculated into the skin during the bite of a blackfly develop into adult worms in 12 to 18 mo. Adult female worms may live up to 15 yr in subcutaneous nodules. Females are 33 to 50 cm long; males are 19 to 42 mm long. Mature female worms produce microfilariae that migrate mainly through the skin and invade the eyes.

Etiology

About 18 million people are infected; about 270,000 are blind and an additional 500,000 are visually impaired. Onchocerciasis is the 2nd leading cause of blindness worldwide (after trachoma). Onchocerciasis is most common in tropical and sub-Saharan regions of Africa. Small foci exist in Yemen, southern Mexico, Guatemala, Ecuador, Colombia, Venezuela, and the Brazilian Amazon. Blindness due to onchocerciasis is fairly rare in the Americas.

Symptoms and Signs

Onchocerciasis typically affects

• Skin (nodules, dermatitis)

• Eyes

Nodules: The subcutaneous (or deeper) nodules (onchocercoma) that contain adult worms may be visible or palpable but are otherwise asymptomatic. They are composed of inflammatory cells and fibrotic tissue in various proportions. Old nodules may caseate or calcify.

Dermatitis: Onchocercal dermatitis is caused by the microfilarial stage of the parasite. Intense pruritus may be the only symptom in lightly infected people. Skin lesions usually consist of a nondescript maculopapular rash with secondary excoriations, scaling ulcerations and lichenification, and mild to moderate lymphadenopathy. Premature wrinkling, skin atrophy, enlargement of inguinal or femoral nodes, lymphatic obstruction, patchy hypopigmentation, and transitory localized areas of edema and erythema can occur.

Onchocercal dermatitis is generalized in most patients, but a localized and sharply delineated form of eczematous dermatitis with hyperkeratosis, scaling, and pigment changes (Sowdah) is common in Yemen and Saudi Arabia.

Eye disease: Ocular involvement ranges from mild visual impairment to complete blindness. Lesions of the anterior portion of the eye include

• Punctate (snowflake) keratitis (an acute inflammatory infiltrate surrounding dying microfilariae that resolves without causing permanent damage)

• Sclerosing keratitis (an ingrowth of fibrovascular scar tissue that may cause subluxation of the lens and blindness)

• Anterior uveitis or iridocyclitis (which may deform the pupil)

Chorioretinitis, optic neuritis, and optic atrophy may also occur.

Diagnosis

• Microscopic examination of a skin sample

Demonstration of microfilariae in skin snips is the traditional diagnostic method (see Table 143-1 on p. 1337). Microfilariae may also be visible in the cornea and anterior chamber of the eye during slit-lamp examination. PCR-based methods to detect parasite DNA in skin snips may be more sensitive than standard techniques but are available only in research settings. Antibody detection is of limited value; there is substantial antigenic cross-reactivity among filaria and other helminths, and a positive serologic test does not distinguish between past and current infection. Palpable nodules (or deep nodules detected by ultrasonography or MRI) can be excised and examined for adult worms, but this procedure is rarely necessary.

Treatment

• Ivermectin

Ivermectin is given as a single oral dose of 150 μg/kg, repeated q 6 to 12 mo until patients are asymptomatic. Ivermectin reduces microfilariae in the skin and eyes and decreases production of microfilariae for many months. It does not appear to kill adult worms in standard regimens but inhibits microfilarial release from female worms. Adverse effects are qualitatively similar to those of diethylcarbamazine (DEC) but are much less common and less severe. DEC is no longer used for onchocerciasis because it can cause a severe hypersensitivity (Mazzotti) reaction, which can further

damage skin and eyes and lead to cardiovascular collapse.

Long-term use (eg, 6 wk) of doxycycline, which targets *Wolbachia* endosymbiont bacteria, with or without a single dose of ivermectin has produced long periods of amicrofilaremia.

Prevention

No drug has been shown to protect against infection with *O. volvulus*. However, annual or semiannual administration of ivermectin effectively controls disease and may decrease transmission. Surgical removal of accessible onchocercomas can also reduce skin microfilaria counts, but it has been replaced by ivermectin therapy.

Simulium bites can be minimized by avoiding fly-infested areas, by wearing protective clothing, and possibly by liberally applying insect repellents.

Hookworm Infection

(Ancylostomiasis)

Ancylostomiasis is infection with the hookworm *Ancylostoma duodenale* or *Necator americanus*. Symptoms include rash at the site of larval entry and sometimes abdominal pain or other GI symptoms during early infection. Later, iron deficiency may develop because of chronic blood loss. Hookworms are a major cause of iron deficiency anemia in endemic regions. Diagnosis is by finding eggs in stool. Treatment is with albendazole, mebendazole, or pyrantel pamoate.

Pathophysiology

Both hookworm species have similar life cycles. Eggs passed in the stool hatch in 1 to 2 days (if they are deposited in a warm, moist place on loose soil) and release rhabditiform larvae, which molt once to become slender filariform larvae in 5 to 10 days. The larvae can survive 3 to 4 wk if environmental conditions are favorable. Filariform larvae penetrate human skin when people walk barefoot on infested soil. The larvae reach the lungs via blood vessels, penetrate into pulmonary alveoli, ascend the bronchial tree to the epiglottis, and are swallowed. The larvae develop into adults in the small bowel; there, they attach to the wall, feeding on blood. Adult worms may live ≥ 2 yr.

Chronic blood loss leads to iron deficiency anemia. Development of anemia depends on worm burden and the amount of absorbable iron in the diet.

Etiology

The estimated prevalence of hookworm infection is about 1 billion, mostly in developing areas. Both *A. duodenale* and *N. americanus* occur in Africa, Asia, and the Americas. Only *A. duodenale* occurs in the Middle East, North Africa, and southern Europe. *N. americanus* predominates in the Americas and Australia; it was once widely distributed in the southern US and is still endemic on islands of the Caribbean and in Central and South America.

Other hookworms: *A. braziliense* and *A. caninum* are hookworms that have cats and dogs as the primary hosts. These hookworms cannot complete their life cycle in humans. If their larvae penetrate human skin, they typically wander in the skin, causing cutaneous larva migrans (), rather than migrate to the intestine.

Rarely, a few *A. caninum* larvae migrate to the intestine, where they may cause eosinophilic enterocolitis. However, they do not cause significant blood loss and anemia, and because they do not mature to full adulthood, they do not lay eggs (making diagnosis difficult). Such intestinal infection may be asymptomatic or cause acute abdominal pain and eosinophilia.

Symptoms and Signs

Hookworm infection is often asymptomatic. However, a pruritic papulovesicular rash (ground itch, cutaneous larva migrans) may develop at the site of larval penetration, usually on the feet. Migration of large numbers of larvae through the lungs occasionally causes Loffler's syndrome, with cough, wheezing, and sometimes hemoptysis. During the acute phase, adult worms in the intestine may cause colicky epigastric pain, anorexia, flatulence, diarrhea, and weight loss. Chronic infection can lead to iron deficiency anemia, and heavy infection can lead to hypoproteinemia, causing pallor, dyspnea, weakness, tachycardia, lassitude, and peripheral edema. A low-grade eosinophilia is often present. Chronic blood loss may lead to severe anemia, heart failure, and anasarca and, in pregnant women, to growth retardation in the fetus.

Diagnosis

• Microscopic examination of stool

A. duodenale and *N. americanus* produce thin-shelled oval eggs that are readily detected in fresh stool. If the stool is not kept cold and examined within several hours, the eggs may hatch and release larvae that may be confused with those of *Strongyloides stercoralis*. Nutritional status, anemia, and iron stores should be evaluated.

Treatment

• Albendazole or mebendazole

Albendazole 400 mg po as a single dose or mebendazole 100 mg po bid for 3 days or 500 mg as a single dose is given. Pyrantel pamoate 11 mg/kg po once/day (1 g maximum) for 3 days is also effective. These drugs should not be used during pregnancy.

General support and correction of iron deficiency anemia are needed if infection is heavy.

Prevention

Preventing unhygienic defecation and avoiding direct skin contact with the soil are effective in preventing infection but difficult to implement in many endemic areas. Periodic mass treatment of susceptible populations at 3- to 4-mo intervals has been used in high-risk areas.

Hookworm treatment for cats and dogs is the primary means for preventing cutaneous larva migrans.

Pinworm Infestation

(Enterobiasis; Oxyuriasis)

Enterobiasis is an intestinal infestation by the pinworm *Enterobius vermicularis*, usually in children. Its major symptom is perianal itching. Diagnosis is by visual inspection for threadlike worms in the perianal area or the cellophane tape test for ova. Treatment is with pyrantel pamoate, mebendazole, or albendazole.

Pinworm infestation is the most common helminthic infection in the US.

Pathophysiology

Infestation usually results from transfer of ova from the perianal area to fomites (clothing, bedding, furniture, rugs, toys), from which the ova are picked up by the new host, transmitted to the mouth, and swallowed. Thumb sucking is a risk factor. Reinfestation (autoinfestation) easily occurs through finger transfer of ova from the perianal area to the mouth. Pinworm infections have also been attributed to anilingus among adults.

Pinworms reach maturity in the lower GI tract within 2 to 6 wk. The female worm migrates to the perianal region (usually at night) to deposit ova. The sticky, gelatinous substance in which the ova are deposited

and the movements of the female worm cause perianal pruritus. The ova can survive on fomites as long as 3 wk at normal room temperature.

Symptoms and Signs

Most infected people have no symptoms or signs, but some experience perianal pruritus and develop perianal excoriations from scratching. Rarely, migrating female worms ascend the human female genital tract, causing vaginitis and, even less commonly, peritoneal lesions.

Many other conditions (eg, abdominal pain, insomnia, seizures) have been attributed to pinworm infestation, but a causal relationship is unlikely. Pinworms have been found obstructing the appendiceal lumen in cases of appendicitis, but the presence of the parasites may be coincidental.

Diagnosis

• Examination of the perianal region for worms, ova, or both

Pinworm infestation can be diagnosed by finding the female worm, which is about 10 mm long (males average 3 mm), in the perianal region 1 or 2 h after a child goes to bed at night or in the morning or by using a low-power microscope to identify ova on cellophane tape. The ova are obtained in the early morning before the child arises by patting the perianal skin-folds with a strip of cellophane tape, which is then placed sticky side down on a glass slide and viewed microscopically. The 50 by 30 μm ova are oval with a thin shell that contains a curled-up larva. A drop of toluene placed between tape and slide dissolves the adhesive and eliminates air bubbles under the tape, which can hamper identification of the ova. This procedure should be repeated on 5 successive mornings if necessary. Eggs may also be encountered, but less frequently, in stool, urine, or vaginal smears.

Treatment

• Mebendazole or albendazole

Because pinworm infestation is seldom harmful, prevalence is high, and reinfestation is common, treatment is indicated only for symptomatic infections. However, most parents actively seek treatment when their children have pinworms.

A single dose of mebendazole 100 mg po (regardless of age) or albendazole 400 mg po, repeated in 2 wk, is effective in eradicating pinworms (but not ova) in > 90% of cases. A single dose of pyrantel pamoate 11 mg/kg po (maximum 1 g) initially and repeated after 2 wk is also effective.

Reinfestation is common because viable ova may be excreted for 1 wk after therapy, and ova deposited in the environment before therapy can survive 3 wk. Multiple infestations within the household are common, and treatment of the entire family may be necessary. Clothing, bedding, and other articles should be washed frequently, and the environment vacuumed.

Carbolated petrolatum or other antipruritic creams or ointments applied to the perianal region may relieve itching.

Strongyloidiasis

(Threadworm Infection)

Strongyloidiasis is infection with *Strongyloides stercoralis*. Findings include rash and pulmonary symptoms (including cough and wheezing), eosinophilia, and abdominal pain with diarrhea. Diagnosis is by finding larvae in stool or small-bowel contents or by detection of antibodies in blood. Treatment is with ivermectin, thiabendazole, or albendazole.

Strongyloidiasis is endemic throughout the tropics and subtropics, including rural areas of the southern US, at sites where bare skin is exposed to contaminated soil and conditions are unsanitary. *Strongyloides*

fulleborni, which infects chimpanzees and baboons, can cause limited infections in humans.

Pathophysiology

Adult worms live in the mucosa and submucosa of the duodenum and jejunum. Released eggs hatch in the bowel lumen, liberating rhabditiform larvae. Most of the larvae are excreted in the stool. After a few days in soil, they develop into infectious filariform larvae. Like hookworms, *Strongyloides* larvae penetrate human skin, migrate via the bloodstream to the lungs, break through pulmonary capillaries, ascend the respiratory tract, are swallowed, and reach the intestine, where they mature in about 2 wk. In the soil, larvae that do not contact humans may develop into free-living adult worms that can reproduce for several generations before their larvae reenter a human host.

Some rhabditiform larvae convert within the intestine to infectious filariform larvae that immediately reenter the bowel wall, short-circuiting the life cycle (internal autoinfection). Sometimes filariform larvae are passed in stool and reenter through the skin of the buttocks and thighs (external autoinfection). Autoinfection explains why strongyloidiasis can persist for many decades and helps account for the extremely high worm burdens in the hyperinfection syndrome.

Hyperinfection may result from a newly acquired *Strongyloides* infection or from activation of a previously asymptomatic one. In either case, it can result in disseminated disease involving organs not usually part of the parasite's normal life cycle (eg, CNS, skin, liver, heart). Hyperinfection usually occurs in patients who are taking corticosteroids or who have impaired cell-mediated immunity, particularly those infected with the human T-lymphotropic virus 1 (HTLV-1). However, hyperinfection and disseminated strongyloidiasis are less common than might be predicted among patients with HIV/AIDS, even those living in areas where *Strongyloides* is highly endemic.

Symptoms and Signs

Infection may be asymptomatic.

Larva currens (creeping infection) is a form of cutaneous larva migrans specific to *Strongyloides* infection; it results from autoinfection. The eruption begins in the perianal region and rapidly spreads, causing intense pruritus, but nonspecific maculopapular or urticarial eruptions may also occur.

Pulmonary symptoms are uncommon, although heavy infections may cause Loffler's syndrome, with cough, wheezing, and eosinophilia. GI symptoms include anorexia, epigastric pain and tenderness, diarrhea, nausea, and vomiting. In heavy infections, malabsorption and protein-losing enteropathy may result in weight loss and cachexia.

Hyperinfection syndrome: GI and pulmonary symptoms are often prominent. Ileus, obstruction, massive GI bleeding, severe malabsorption, and peritonitis may occur. Pulmonary symptoms include dyspnea, hemoptysis, and respiratory failure. Infiltrates may be seen on chest x-ray.

Other symptoms depend on the organ involved. CNS involvement includes parasitic meningitis, brain abscess, and diffuse invasion of the brain. Secondary gram-negative meningitis and bacteremia, which occurs with high frequency, probably reflect disruption of bowel mucosa, carriage of bacteria on migrating larvae, or both. Liver infection may result in cholestatic and granulomatous hepatitis. Infection may be fatal in immunocompromised patients, even with treatment.

Diagnosis

• Microscopic examination of stool

• Sometimes enzyme immunoassay

Microscopic examination of a single stool sample detects larvae in about 25% of uncomplicated infections. Repeated examination of concentrated stool or the agar-plate method raises sensitivity to ≥ 85%. If the specimen stands at room temperature for several hours, rhabditiform larvae may transform

into longer filariform larvae, leading to erroneous diagnosis of hyperinfection. Sampling of the proximal small bowel by aspiration may be positive in low-level infections and should be done endoscopically to permit biopsy of suspicious duodenal and jejunal lesions. In hyperinfection syndrome, filariform larvae may be found in stool, duodenal contents, sputum, and bronchial washings and, uncommonly, in CSF, urine, or pleural or ascitic fluid. Chest x-rays may show diffuse interstitial infiltrates, consolidation, or abscess.

Several immunodiagnostic tests are available for strongyloidiasis. Enzyme immunoassay (EIA) is recommended because of its greater sensitivity (> 90%). IgG antibodies can usually be detected even in immunocompromised patients with disseminated strongyloidiasis. Cross-reactions in patients with filariasis or other nematode infections may result in false-positive tests. Antibody test results cannot be used to differentiate current from past infection. A positive test warrants continuing efforts to establish a parasitologic diagnosis. Serologic monitoring may be useful in follow-up because antibody levels decrease within 6 mo of successful chemotherapy.

Eosinophilia is often present but can be suppressed by drugs such as corticosteroids or cytotoxic chemotherapeutic drugs.

Treatment

• Ivermectin

Ivermectin 200 μg/kg po once/day for 2 days is used for uncomplicated infection and is generally well tolerated. Albendazole 400 mg po bid for 7 days is an alternative. In immunocompromised patients, prolonged therapy or repeated courses may be needed. Combined therapy with albendazole and ivermectin has been used for hyperinfections. In severely ill patients who are unable to take oral drugs, veterinary parenteral or rectal preparations of ivermectin have been used.

Cure should be documented by repeated stool examinations.

Prevention

Prevention of primary infections is the same as for hookworms. To prevent potentially fatal hyperinfection syndrome, clinicians should do several stool examinations and serologic testing in patients with possible exposure to *Strongyloides* (even in the distant past), with unexplained eosinophilia, or with symptoms that suggest strongyloidiasis before corticosteroids or other immunosuppressants are used. If patients are infected, treatment for strongyloidiasis should be instituted and parasitologic cure should be documented before immunosuppression. Immunosuppressed people who have recurrent strongyloidiasis require additional courses of treatment until cured.

Toxocariasis

(Visceral or Ocular Larva Migrans)

Toxocariasis is human infection with nematode ascarid larvae that ordinarily infect animals. Symptoms are fever, anorexia, hepatosplenomegaly, rash, pneumonitis, asthma, or visual impairment. Diagnosis is by enzyme immunoassay. Treatment is with albendazole or mebendazole. Corticosteroids may be added for severe symptoms or eye involvement.

Pathophysiology

The eggs of *Toxocara canis, T. cati*, and other animal ascarid helminths mature in soil and infect dogs, cats, and other animals. Humans may accidentally ingest eggs in soil contaminated by stool from infected animals or may ingest infected transfer hosts (eg, rabbits). The eggs hatch in the human intestine. Larvae penetrate the bowel wall and may migrate through the liver, lungs, CNS, eyes, or other tissues. Tissue damage is caused by focal eosinophilic granulomatous reactions to the migrating larvae. The larvae usually do not complete their development in the human body but can remain alive for many months.

Symptoms and Signs

Visceral larva migrans (VLM): This syndrome consists of fever, anorexia, hepatosplenomegaly, rash, pneumonitis, and asthmatic symptoms, depending on the affected organs.

VLM occurs mostly in 2- to 5-yr-old children with a history of geophagia. The syndrome is self-limiting in 6 to 18 mo if egg intake ceases. Deaths due to invasion of the brain or heart occur rarely.

Ocular larva migrans (OLM): This syndrome, also called ocular toxocariasis, usually has no or very mild systemic manifestations. OLM lesions consist mostly of granulomatous reactions to a larva in the retina; the larva may cause visual impairment.

OLM occurs in older children and less commonly in young adults. The lesion may be confused with retinoblastoma or other intraocular tumors.

Diagnosis

• Enzyme immunoassay plus clinical findings

Diagnosis is based on clinical, epidemiologic, and serologic findings. Enzyme immunoassay (EIA) is currently recommended. Isoagglutinins are frequently elevated, but this finding is nonspecific. Hyperglobulinemia, leukocytosis, and marked eosinophilia are common.

Biopsies of the liver or other affected organs may show eosinophilic granulomatous reactions, but larvae are difficult to find in tissue sections and biopsies are low yield. Stool examinations are worthless. OLM should be distinguished from retinoblastoma to prevent unnecessary surgical enucleation of the eye.

Treatment

• Mebendazole or albendazole

• Symptomatic treatment

Mebendazole 100 to 200 mg po bid for 5 days or albendazole 400 mg po bid for 5 days is often used, but the optimal duration of therapy has not been determined.

Antihistamines may suffice for mild symptoms. Corticosteroids (prednisone 20 to 40 mg po once/day) are indicated for patients with severe symptoms. Corticosteroids, both local and oral, are also indicated for acute OLM.

Laser photocoagulation has been used to kill larvae in the retina.

Prevention

Infection with *T. canis* in puppies is common in the US; infection with *T. cati* in cats is less common. Both animals should be dewormed regularly. Contact with dirt or sand contaminated with animal feces should be minimized. Sandboxes should be covered.

Baylisascariasis

Baylisascariasis is infection with the raccoon ascarid, *Baylisascaris procyonis*, which may cause fatal CNS infection in humans.

Infection usually occurs in children who play in dirt or with articles contaminated with raccoon feces. It occurs in the US, particularly in the Middle Atlantic, Midwest, and Northeast. Although baylisascariasis is rare in people, it is of concern because a large number of raccoons live near humans and the infection rate of *B. procyonis* in these animals is high.

Migration of the larvae through a wide variety of tissues (liver, heart, lungs, brain, eyes) results in VLM and OLM syndromes, similar to those due to toxocariasis. However, in contrast to *Toxocara* larvae, *Baylisascaris* larvae continue to grow to a large size (up to 24 cm for females and 12 cm for males) within the CNS and cause eosinophilic meningoencephalitis. Tissue damage and symptoms and signs of baylisascariasis are often severe because *Baylisascaris* larvae continue to grow, tend to wander widely, and do not readily die.

Diagnosis is difficult because serologic tests are not widely available. Viewing a larva during ocular examination is often a clue.

Treatment is similar to that of other causes of VLM and OLM.

Trichinosis

(Trichiniasis)

Trichinosis is infection with *Trichinella spiralis* or related *Trichinella* species. Symptoms include initial GI irritation followed by periorbital edema, muscle pain, fever, and eosinophilia. Diagnosis is clinical and with serologic tests. Muscle biopsy may be diagnostic but is seldom necessary. Treatment is with mebendazole or albendazole plus prednisone if symptoms are severe.

Trichinosis occurs worldwide. In addition to the classic agent *Trichinella spiralis*, trichinosis can be caused by *T. pseudospiralis, T. nativa, T. nelsoni*, and *T. britovi* in different geographic locations.

Pathophysiology

The life cycle is maintained by animals that are fed (eg, pigs, horses) or eat (eg, bears, foxes, boars) other animals whose striated muscles contain encysted infective larvae (eg, rodents). Humans become infected by eating raw, undercooked, or processed meat from infected animals, most commonly pigs, wild boar, or bear. Larvae excyst in the small bowel, penetrate the mucosa, and become adults in 6 to 8 days. Females are about 2.2 mm long, and males are about 1.2 mm long. Mature females release living larvae for 4 to 6 wk and then die or are expelled. Newborn larvae migrate through the bloodstream and body but ultimately survive only within striated skeletal muscle cells. Larvae fully encyst in 1 to 2 mo and remain viable for several years as intracellular parasites. Dead larvae eventually are resorbed or calcify. The cycle continues only if encysted larvae are ingested by another carnivore.

Symptoms and Signs

Many infections are asymptomatic or mild. During the 1st wk, nausea, abdominal cramps, and diarrhea may occur. One to 2 wk after infection, systemic symptoms and signs begin: facial or periorbital edema, myalgia, persistent fever, headache, and subconjunctival hemorrhages and petechiae. Eye pain and photophobia often precede myalgia.

Symptoms due to muscle invasion may mimic polymyositis. The muscles of respiration, speech, mastication, and swallowing may be painful. Severe dyspnea may occur in heavy infections.

Fever is generally remittent, rising to 39° C or higher, remaining elevated for several days, and then falling gradually. Eosinophilia usually begins when newborn larvae invade tissues, peaks 2 to 4 wk after infection, and gradually declines as the larvae encyst.

In heavy infections, the inflammation may cause complications: cardiac (myocarditis, heart failure, arrhythmia), neurologic (encephalitis, meningitis, visual or auditory disorders, seizures), or pulmonary (pneumonitis, pleurisy). Death may result from myocarditis or encephalitis.

Symptoms and signs gradually resolve, and most disappear by about the 3rd mo, when the larvae have become fully encysted in muscle cells and eliminated from other organs and tissues. Vague muscular pains and fatigue may persist for months. Recurrent infections with *T. nativa* in northern latitudes can cause chronic diarrhea.

Diagnosis

• Enzyme immunoassay

• Rarely biopsy

No specific tests to diagnose the intestinal stage are available. After the 2nd wk of infection, a muscle biopsy may detect larvae and cysts but is seldom necessary. Diffuse inflammation in muscle tissue indicates recent infection.

A number of serologic tests have been used, but enzyme immunoassay (EIA) using *T. spiralis* excretory-secretory (ES) antigen seems to be the quickest way to detect the infection and is used in the US. Antibodies are often not detectable for the first 3 to 5 wk of infection, so tests should be repeated at weekly intervals if results are initially negative. Because antibodies may persist for years, serologic tests are of most value if they are initially negative and then positive. Serologic tests and muscle biopsy are complementary tests: Either one can be negative in a given patient with trichinosis. Skin testing with larval antigens is unreliable.

Muscle enzymes (creatine kinase and LDH) are elevated in 50% of patients and correlate with abnormal electromyograms.

Trichinosis must be differentiated from

• Acute rheumatic fever, acute arthritis, angioedema, and myositis

• Febrile illnesses such as TB, typhoid fever, sepsis, and undulant fever

• Pneumonitis

• Neurologic manifestations of meningitis, encephalitis, and poliomyelitis

• Eosinophilia due to Hodgkin lymphoma, eosinophilic leukemia, polyarteritis nodosa, or disease caused by other migrating nematodes

Treatment

• Symptomatic treatment

• Mebendazole or albendazole to eliminate adult worms

Anthelmintics eliminate adult worms from the GI tract but probably have little effect on encysted larvae. Mebendazole 200 to 400 mg po tid for 3 days, then 400 to 500 mg tid for 10 days or albendazole 400 mg bid for 8 to 14 days may be used.

Analgesics (eg, NSAIDs, opioids) may help relieve muscle pains. For severe allergic manifestations or myocardial or CNS involvement, prednisone 20 to 60 mg po once/day is given for 3 or 4 days, then tapered over 10 to 14 days.

Prevention

Trichinosis is prevented by cooking meat thoroughly until brown (71° C [160° F] throughout). Larvae can usually be killed by freezing the meat at -17° C (1° F) for 3 wk or -30° C (-22° F) for 6 days, but *T. nativa* is relatively resistant. Smoking, microwave cooking, or salting meat does not reliably kill larvae.

Domestic swine should not be fed uncooked meat products.

Trichuriasis

(Whipworm Infection; Trichocephaliasis)

Trichuriasis is infection with *Trichuris trichiura*. Symptoms may include abdominal pain, diarrhea, and, in heavy infections, anemia and undernutrition. Diagnosis is by finding eggs in stool. Treatment is with mebendazole or albendazole.

Infection is spread via the fecal-oral route. Ingested eggs hatch and enter the crypts of the small bowel as larvae. After maturing for 1 to 3 mo, the worms migrate to the cecum and ascending colon, where they attach to the superficial epithelium, mate, and lay eggs.

Adult worms may live 7 to 10 yr.

Trichuriasis is the 3rd most common roundworm infection. An estimated 800 million people are infected worldwide. *Trichuris trichiura* occurs principally in developing tropical or subtropical areas, but infections also occur in the southern US. Children are most affected.

Light infections are often asymptomatic. Heavy infections cause abdominal pain, anorexia, and diarrhea and may result in anemia or retarded growth. Very heavy infections may cause weight loss, anemia, and rectal prolapse, particularly in children.

Diagnosis

• Microscopic examination of stool

Diagnosis is made by microscopic examination of stool; the characteristic lemon-shaped eggs with clear opercula at both ends are readily apparent. When colonoscopy is done for other indications, wiggling adult worms may be seen protruding into the bowel lumen. CBC is done to check for anemia.

Treatment

• Mebendazole

Mebendazole 100 mg po bid for 3 days or 500 mg as a single dose is recommended. Alternatively, albendazole 400 mg po once/day for 3 days or ivermectin 200 μg/kg po once/day for 3 days may be used. These drugs should not be used during pregnancy.

Prevention is possible through good sanitation and personal hygiene.

Chapter 145. Trematodes (Flukes)

Introduction

Flukes are parasitic flatworms that infect the blood vessels, GI tract, lungs, or liver. They are often categorized according to the organ system they invade:

• *Schistosoma* sp: Vasculature of the GI or GU system

• *Fasciolopsis buski, Heterophyes heterophyes*, and related organisms: Lumen of the GI tract

• *Clonorchis sinensis, Fasciola hepatica*, and *Opisthorchis* sp: Liver

• *Paragonimus westermani* and related species: Lungs and other organs such as the CNS

Clonorchiasis

(Oriental Liver Fluke Infection)

Clonorchiasis is infection with the liver fluke *Clonorchis sinensis*. Infection is acquired by eating undercooked freshwater fish. Symptoms include fever, chills, epigastric pain, tender hepatomegaly, diarrhea, and mild jaundice. Diagnosis is by identifying eggs in the feces or duodenal contents. Treatment is with praziquantel or albendazole.

Clonorchis is endemic in the Far East, especially in Korea, Japan, Taiwan, and southern China, and infection occurs elsewhere among immigrants and people eating fish imported from endemic areas.

Pathophysiology

Adult *C. sinensis* worms live in the bile ducts. Eggs are passed in the stool and ingested by snails. Cercariae (free-swimming larvae) released from infected snails subsequently infect a variety of freshwater fish. Humans become infected by eating raw, dried, salted, or pickled fish containing encysted metacercariae (resting or maturing stage). Metacercariae are released in the duodenum, enter the common bile duct through the ampulla of Vater, and migrate to smaller intrahepatic ducts (or occasionally the gallbladder and pancreatic ducts), where they mature into adult worms in about 1 mo. The adults may live ≥ 20 yr and grow to about 10 to 25 mm by 3 to 5 mm.

Symptoms and Signs

Light infections are usually asymptomatic. Heavier infections can cause fever, chills, epigastric pain, tender hepatomegaly, mild jaundice, and eosinophilia. Later, diarrhea may occur. Chronic cholangitis in heavy infections may progress to atrophy of liver parenchyma, portal fibrosis, and cirrhosis. Jaundice may occur if a mass of flukes obstructs the biliary tree. Other complications include suppurative cholangitis, chronic pancreatitis, and, late in the course, cholangiocarcinoma.

Diagnosis

• Microscopic examination of stool

Diagnosis is by finding eggs in the feces or duodenal contents. The eggs are difficult to distinguish from those of *Metagonimus, Heterophyes*, and *Opisthorchis*. Occasionally, the diagnosis is made by identifying adult flukes in surgical specimens or by doing percutaneous transhepatic cholangiography.

Other tests are nondiagnostic but may be abnormal; alkaline phosphatase, bilirubin, and eosinophil counts may be elevated. A plain abdominal x-ray occasionally shows intrahepatic calcification. Hepatic ultrasonography may show ductal irregularities and evidence of scarring.

Treatment

• Praziquantel or albendazole

Treatment is with praziquantel 25 mg/kg po tid for 2 days or albendazole 10 mg/kg po once/day for 7 days. Biliary obstruction may require surgery. Freshwater fish from endemic waters should be thoroughly cooked and not eaten raw, pickled, or wine-soaked.

Fascioliasis

Fascioliasis is infection with the liver fluke *Fasciola hepatica*, which is acquired by eating contaminated watercress or other water plants.

F. hepatica is the sheep and cattle liver fluke. Incidental human fascioliasis, acquired by eating watercress contaminated by sheep or cattle dung, occurs in Europe, Africa, China, and South America but is rare in the US.

In acute infection, immature flukes migrate through the intestinal wall, the peritoneal cavity, the liver capsule, and the parenchyma of the liver before entering the biliary ducts where they mature to adulthood in about 3 to 4 mo.

Acute infection causes abdominal pain, hepatomegaly, nausea, vomiting, intermittent fever, urticaria, eosinophilia, malaise, and weight loss due to liver damage. Chronic infection may be asymptomatic or lead to intermittent biliary tract obstruction. Ectopic lesions may occur in the intestinal wall, lungs, or other organs.

CT frequently shows hypodense lesions in the liver. Antibody detection assays are useful in the early stages of disease. Eggs may be recovered in the stool or, during chronic infection, in duodenal or biliary materials.

Treatment is with triclabendazole (10 mg/kg po once or twice) where it is available. Alternatively, nitazoxanide 500 mg bid po for 7 days or bithionol 30 to 50 mg/kg po every other day for 10 to 15 doses may be used. Treatment failures are common with praziquantel.

Fasciolopsiasis

Fasciolopsiasis is infection with the intestinal fluke *Fasciolopsis buski*, which is acquired by eating aquatic plants.

F. buski is present in the intestine of pigs in many parts of Asia. Human infection is acquired by eating aquatic plants (eg, water chestnuts) that bear infectious metacercariae (encysted stage). Adult worms attach to and ulcerate the mucosa of the proximal small bowel. They grow to about 20 to 75 mm by 8 to 20 mm. Adults have a life span of about 1 yr.

Most infections are light and asymptomatic, but heavy infections may cause diarrhea, abdominal pain, and signs of malabsorption.

Diagnosis is made by finding eggs or, less commonly, adult worms in the feces.

Treatment is with praziquantel 25 mg/kg po tid for 1 day.

Heterophyiasis and Related Trematode Infections

Heterophyiasis is infection with the intestinal fluke *Heterophyes heterophyes*, which is acquired by eating infected raw or undercooked fish from freshwater or brackish water.

Heterophyes heterophyes and several related trematodes are endemic in the Far East, Middle East, and Egypt. Infection is acquired by eating infected raw or undercooked fish from freshwater or brackish water

containing metacercariae (encysted stage). After ingestion, metacercariae excyst and attach to the mucosa of the small intestine. There, they develop into adults, growing to about 1.0 to 1.7 mm by 0.3 to 0.4 mm. Salmon live part of their lives in freshwater and can be infected with *Nanophyetus salmincola*.

Adult flukes can cause abdominal pain and diarrhea. Diagnosis is by finding eggs in the feces. Treatment is with praziquantel 25 mg/kg po tid for 1 day.

Opisthorchiasis

Opisthorchiasis is infection with 1 of 2 species of the liver fluke *Opisthorchis*, which is acquired by eating infected raw or undercooked fish.

Opisthorchiasis occurs in cats and dogs in eastern and central Europe, Siberia, and parts of Asia, such as Thailand and Cambodia. The life cycle of *Opisthorchis* requires both snails and fish. Human disease resembles clonorchiasis and is acquired by eating raw or undercooked freshwater fish that contains infectious metacercariae (encysted stage). After ingestion, metacercariae excyst and ascend through the ampulla of Vater into the biliary ducts, where they attach to the mucosa and mature. Adult flukes grow to 5 to 10 mm by 1 to 2 mm (*O. viverrini*) or 7 to 12 mm by 2 to 3 mm (*O. felineus*).

Symptoms include vague GI discomfort or bowel symptoms (diarrhea or constipation). Rarely, infection causes cholangitis or cholangiocarcinoma.

Diagnosis is by finding eggs in the feces. Praziquantel 25 mg/kg po tid for 2 days is the treatment of choice.

Paragonimiasis

(Oriental Lung Fluke Infection; Endemic Hemoptysis)

Paragonimiasis is infection with the lung fluke *Paragonimus westermani* and related species. Humans are infected by eating raw, pickled, or poorly cooked freshwater crustaceans. Symptoms include chronic cough, chest pain, dyspnea, and hemoptysis. Allergic skin reactions and CNS abnormalities due to ectopic flukes, including seizures, aphasia, paresis, and visual disturbances, can also occur. Diagnosis is by identifying eggs in sputum, stool, or pleural or peritoneal fluid. Serologic tests are also available. Praziquantel is the treatment of choice; bithionol is an alternative.

Although > 30 species of *Paragonimus* exist and 10 have been reported to infect humans, *P. westermani* is the most frequent cause of disease. The most important endemic areas are in the Far East, principally Korea, Japan, Taiwan, the highlands of China, and the Philippines. Endemic foci also exist in West Africa and in parts of South and Central America.

Pathophysiology

Eggs passed in sputum or feces develop for 2 to 3 wk in freshwater before miracidia (first larval stage) hatch. The miracidia invade snails; there, they develop, multiply, and eventually emerge as cercariae (free-swimming larvae). Cercariae penetrate freshwater crabs or crayfish and encyst to form metacercariae. Humans become infected by eating raw, pickled, or poorly cooked crustaceans. Metacercariae excyst in the human GI tract, penetrate the intestinal wall, move into the peritoneal cavity, then through the diaphragm into the pleural cavity; they enter lung tissue, encyst, and develop into hermaphroditic adult worms, which grow to about 7.5 to 12 mm by 4 to 6 mm. Worms may also reach the brain, liver, lymph nodes, skin, and spinal cord and develop there. However, in these organs, the life cycle cannot be completed because the eggs have no way to exit the body. Adult flukes may persist for 20 to 25 yr.

Other hosts include pigs, dogs, and a variety of feline species.

Symptoms and Signs

Most damage is to the lungs, but other organs may be involved. About 25 to 45% of all extrapulmonary infections affect the CNS. Manifestations of pulmonary infection develop slowly and include chronic cough, chest pain, hemoptysis, and dyspnea; the clinical picture resembles and is often confused with TB. Cerebral infections manifest as space-occupying lesions, often within a year after the onset of pulmonary disease. Seizures, aphasia, paresis, and visual disturbances occur. Migratory allergic skin lesions similar to those of cutaneous larva migrans are common in infections with *P. skrjabini* but also occur with other species.

Diagnosis

• Microscopic examination of sputum and stool

Diagnosis is by identifying the characteristic large operculated eggs in sputum or stool. Occasionally, eggs may be found in pleural or peritoneal fluid. Eggs may be difficult to find because they are released intermittently and in small numbers. Concentration techniques increase sensitivity.

X-rays provide ancillary information but are not diagnostic; chest x-rays and CT may show a diffuse infiltrate, nodules and annular opacities, cavitations, lung abscesses, pleural effusion, and pneumothorax. Serologic tests may assist in diagnosis of light or extrapulmonary infections.

Treatment

• Praziquantel

Praziquantel 25 mg/kg po tid for 2 days cures 80 to 100% of pulmonary infections and is the drug of choice. Bithionol 30 to 50 mg/kg po every other day for 10 to 15 doses is an alternative but has more adverse effects. Praziquantel is used to treat extrapulmonary infections, but multiple courses may be required. Surgery may be needed to excise skin lesions or, rarely, brain cysts.

The best prevention is to avoid eating raw or undercooked freshwater crabs and crayfish from endemic waters.

Schistosomiasis

(Bilharziasis)

Schistosomiasis is infection with blood flukes of the genus *Schistosoma*, which are acquired transcutaneously by swimming or wading in contaminated freshwater. The organisms infect the vasculature of the GI or GU system. Acute symptoms are dermatitis, followed several weeks later by fever, chills, nausea, abdominal pain, diarrhea, malaise, and myalgia. Chronic symptoms vary with species but include bloody diarrhea (eg, with *S. mansoni*) or hematuria (eg, with *S. haematobium*). Diagnosis is by identifying eggs in stool, urine, or biopsy specimens. Serologic tests may be sensitive and specific but do not provide information about the worm burden or clinical status. Treatment is with praziquantel.

Etiology

Schistosomiasis is by far the most important trematode infection. *Schistosoma* is the only trematode that invades through the skin; all other trematodes infect only via ingestion. About 200 million people are infected worldwide. The risk of infection is spreading as new dams are built in endemic areas.

Five species of schistosomes infect humans; all have similar life cycles involving freshwater snails. *S. haematobium* causes urinary tract disease; the other *Schistosoma* sp cause intestinal disease. Geographic distribution differs by species:

• *S. haematobium:* Widely distributed over the African continent with smaller foci in the Middle East and India

- *S. mansoni:* Widespread in Africa and the only species in the Western Hemisphere, endemic in Brazil, Surinam, and Venezuela and on some Caribbean islands

- *S. japonicum:* Only in Asia, mainly in China and the Philippines

- *S. mekongi:* Laos and Cambodia

- *S. intercalatum:* Central Africa

The disease may be imported in travelers and immigrants from endemic areas, but transmission does not occur within the US and Canada.

Pathophysiology

Adult worms live and copulate within the veins of the mesentery (typically *S. japonicum* and *S. mansoni*) or bladder (typically *S. haematobium*—see Fig. 145-1). Some eggs penetrate the intestinal or bladder mucosa and are passed in stool or urine; other eggs remain within the host organ or are transported through the portal system to the liver and occasionally to other sites (eg, lungs, CNS, spinal cord). Excreted eggs hatch in freshwater, releasing miracidia (first larval stage), which enter snails. After multiplication, thousands of free-swimming cercariae are released. Cercariae penetrate human skin within a few minutes after exposure and transform into schistosomula, which travel through the bloodstream to the liver, where they mature into adults. The adults then migrate to their ultimate home in the intestinal veins or the venous plexus of the GU tract.

Eggs appear in stool or urine 1 to 3 mo after cercarial penetration.

Estimates of the adult worm life span range from 3 to 7 yr. The females range in size from 7 to 20 mm; males are slightly smaller.

Symptoms and Signs

Schistosome dermatitis: This pruritic papular rash (see also Dermatitis Caused by Avian and Animal Schistosomes on p. 1360) develops where the cercariae penetrate the skin in previously sensitized people.

Acute schistosomiasis: Acute schistosomiasis (Katayama fever) occurs with onset of egg laying, typically 2 to 4 wk after heavy exposure. Symptoms include fever, chills, cough, nausea, abdominal pain, malaise, myalgia, urticarial rashes, and marked eosinophilia, resembling serum sickness. Manifestations are more common and usually more severe in visitors than in residents of endemic areas and typically last for several weeks.

Chronic schistosomiasis: Chronic schistosomiasis results mostly from host responses to eggs retained in tissues. Early on, intestinal mucosal ulcerations caused by *S. mansoni* or *S. japonicum* may bleed and result in bloody diarrhea. As lesions progress, focal fibrosis, strictures, fistulas, and papillomatous growths may develop. With *S. haematobium,* ulcerations in the bladder wall may cause dysuria, hematuria, and urinary frequency. Over time, chronic cystitis develops. Strictures may lead to hydroureter and hydronephrosis. Papillomatous masses in the bladder are common, and squamous cell carcinoma may develop. Blood loss from both GI and GU tracts frequently results in anemia.

Secondary bacterial infection of the GU tract is common, and persistent *Salmonella* septicemia may occur with *S. mansoni*. Several species, notably *S. haematobium,* can cause genital disease in both men and women, resulting in numerous symptoms including infertility.

[**Fig. 145-1.** Simplified *Schistosoma* life cycle.]

Granulomatous reactions to eggs of *S. mansoni* and *S. japonicum* in the liver usually do not compromise

liver function but may cause fibrosis and cirrhosis, which can lead to portal hypertension and subsequent hematemesis due to esophageal varices. Eggs in the lungs may produce granulomas and focal obliterative arteritis, which may cause pulmonary hypertension and cor pulmonale. Eggs lodged in the spinal cord can cause transverse myelitis, and those in the CNS can cause seizures.

Diagnosis

• Microscopic examination of stool

Stool (*S. japonicum, S. mansoni, S. mekongi, S. intercalatum*) or urine (*S. haematobium*, occasionally *S. japonicum*) is examined for eggs. Repeated examinations using concentration techniques may be necessary. Geography is a primary determinant of species, so a history of exposure should be communicated to the laboratory. If the clinical picture suggests schistosomiasis but no eggs are found after repeated examination of urine or feces, intestinal or bladder mucosa can be biopsied to check for eggs.

Depending on the antigens used, serologic tests may be sensitive and specific for infection, but they do not provide information about worm burden, clinical status, or prognosis.

Treatment

• Praziquantel

Single-day oral treatment with praziquantel (20 mg/kg bid for *S. haematobium, S. mansoni*, and *S. intercalatum*; 20 mg/kg tid for *S. japonicum* and *S. mekongi*) is recommended. However, treatment does not affect developing schistosomula and thus may not abort an early infection. Adverse effects are generally mild and include abdominal pain, diarrhea, headache, and dizziness. Therapeutic failures have been reported, but it is difficult to determine whether they are due to reinfection or drug-resistant strains.

Oxamniquine (not available in the US) has been effective in treating infection due to *S. mansoni* in some areas where praziquantel has been less effective. African strains are more resistant to this drug than South American strains and require higher doses.

Patients should be examined for living eggs 3 and 6 mo after treatment. Retreatment is indicated if egg excretion has not decreased markedly.

Prevention

Scrupulously avoiding contact with contaminated freshwater prevents infection. The sanitary disposal of urine and feces reduces the likelihood of infection. Adult residents of endemic areas are more resistant to reinfection than children, suggesting the possibility of acquired immunity. Vaccine development is under way.

Dermatitis Caused by Avian and Animal Schistosomes

(Cercarial Dermatitis; Clam Diggers' Itch; Swimmers' Itch)

Cercarial dermatitis, a skin condition, occurs when *Schistosoma* sp that cannot develop in humans penetrate the skin during contact with contaminated freshwater or brackish water.

Cercariae of *Schistosoma* sp that infect birds and mammals other than humans can penetrate the skin. Although the organisms do not develop in humans, humans may become sensitized and develop pruritic maculopapular, then vesicular skin lesions at the site of penetration. Skin lesions may be accompanied by a systemic febrile response that runs for 5 to 7 days and resolves spontaneously.

Ocean-related schistosome dermatitis (clam diggers' itch) occurs on all Atlantic, Gulf, Pacific, and Hawaiian coasts. It is very common in muddy flats off Cape Cod. Freshwater schistosome dermatitis (swimmers' itch) is common in the lakes of northern Michigan, Wisconsin, and Minnesota.

Diagnosis is based on clinical findings. Most cases do not require medical attention.

Treatment is symptomatic with cool compresses, baking soda, or antipruritic lotions. Topical corticosteroids can also be used.

Chapter 146. Cestodes (Tapeworms)

Introduction

All tapeworms (cestodes) cycle through 3 stages—eggs, larvae, and adults. Adults inhabit the intestines of definitive hosts, mammalian carnivores. Several of the adult tapeworms that infect humans are named after their intermediate host: the fish tapeworm (*Diphyllobothrium latum*), the beef tapeworm (*Taenia saginata*), and the pork tapeworm (*Taenia solium*). Eggs laid by adult tapeworms living in the intestines of definitive hosts are excreted with feces into the environment and ingested by an intermediate host (typically another species), in which larvae develop, enter the circulation, and encyst in the musculature or other organs. When the intermediate host is eaten, cysts develop into adult tapeworms in the intestines of the definitive host, restarting the cycle. With some cestode species (eg, *T. solium*), the definitive host can also serve as an intermediate host; tissue cysts develop instead of intestinal worms after eggs are ingested.

Adult tapeworms are multisegmented flat worms that lack a digestive tract and absorb nutrients directly from the host's small bowel. In the host's digestive tract, adult tapeworms can become large; the longest parasite in the world is the 40-m whale tapeworm, *Polygonoporus* sp. Tapeworms have 3 recognizable portions. The scolex (head) functions as an anchoring organ that attaches to intestinal mucosa. The neck is an unsegmented region with high regenerative capacity. If treatment does not eliminate the neck and scolex, the entire worm may regenerate. The rest of the worm consists of numerous proglottids (segments). Proglottids closest to the neck are undifferentiated. As proglottids move caudally, each develops hermaphroditic sex organs. Distal proglottids are gravid and contain eggs in a uterus.

In contrast to adult tapeworms, larvae can cause severe and even lethal disease, most importantly in the brain, but also in the liver, lungs, eyes, muscles, and subcutaneous tissues. In humans, *T. solium* causes cysticercosis, and *Echinococcus granulosus* and *E. multilocularis* cause hydatid disease. *Sparganum mansoni* and *T. multiceps* larvae can also infect humans.

Symptoms and Signs

Adult tapeworms are so well adapted to their hosts that they cause minimal symptoms. *Hymenolepis nana* is an exception and can cause abdominal discomfort, diarrhea, and weight loss. However, larvae may elicit intense immunologic reactions as they travel through tissues (hence inducing immunity) and cause severe disease when they settle in extraintestinal sites.

Diagnosis

Adult tapeworm infections are diagnosed by identifying eggs or gravid proglottid segments in stool. Larval disease is best identified by imaging (eg, brain CT or MRI) and, for some species, serologic tests.

Treatment

The anthelmintic drugs, praziquantel and niclosamide, are effective for most intestinal tapeworm infections. Some extraintestinal infections respond to anthelmintic treatment; others require surgical intervention.

Prevention

Prevention and control involve the following:

• Thorough cooking (to a temperature > 57° C [> 135° F]) of pork, beef, lamb, game meat, and fish

• Regular worming of dogs and cats

• Prevention of recycling through hosts (eg, dogs eating dead game or livestock)

• Reduction and avoidance of intermediate hosts such as rodents, fleas, and grain beetles

• Meat inspection

• Sanitary treatment of human waste

Prolonged freezing of meat is effective, pickling is variably effective, and smoking and drying are ineffective.

Diphyllobothriasis

(Fish Tapeworm Infection)

Diphyllobothriasis is infection with the intestinal tapeworm, *Diphyllobothrium latum*, a parasite of freshwater fish. Treatment is with praziquantel.

D. latum is the largest parasite of humans (up to 10 m in length). It and *Sparganum mansoni* are the only human tapeworms with aquatic life cycles. In freshwater, eggs of *D. latum* from human feces hatch into free-swimming larvae, which are ingested by microcrustaceans. The microcrustaceans are ingested by fish, in which the larvae become infective.

Diphyllobothriasis occurs worldwide, especially where cool lakes are contaminated by sewage. Infections in the US and northern Europe occur in people who eat raw freshwater fish. Infection is less common with current sewage treatment.

Infection is usually asymptomatic, but mild GI symptoms may be noted. Fish tapeworms take up dietary vitamin B_{12}, occasionally resulting in vitamin B_{12} deficiency and megaloblastic anemia.

Diagnosis is by identification of characteristic operculated eggs or broad proglottids in stool.

Treatment

• Praziquantel or niclosamide

Treatment is with a single oral dose of praziquantel 5 to 10 mg/kg. Alternatively, a single 2-g dose of niclosamide is given as 4 tablets (500 mg each) that are chewed one at a time and swallowed. For children, the dose is 50 mg/kg once.

Vitamin B_{12} may be needed to correct the anemia. Thorough cooking of freshwater fish or freezing it at -10° C (14° F) for 48 h prevents infection.

Dipylidium caninum Infection

Dipylidium caninum can cause intestinal infection, which is typically asymptomatic.

D. caninum, the double-pored tapeworm, is present in dogs and cats. Fleas are the intermediate host. Ingestion of an infected flea, usually by a young child, causes an asymptomatic, self-limited infection, but proglottids may be seen in stool.

Treatment is with a single oral dose of praziquantel 5 to 10 mg/kg. Alternatively, a single 2-g dose of niclosamide is given as 4 tablets (500 mg each) that are chewed one at a time and swallowed. For children, the dose is 50 mg/kg once.

Echinococcosis

(Hydatid Disease)

Echinococcosis is infection with larvae of *Echinococcus granulosus* or *E. multilocularis* (alveolar hydatid disease). Symptoms depend on the organ involved—eg, jaundice and abdominal discomfort with liver cysts or cough, chest pain, and hemoptysis with lung cysts. Cyst rupture can cause fever, urticaria, and serious anaphylactic reactions. Diagnosis is with imaging, examination of cyst fluid, or serologic tests. Treatment is with albendazole, surgery, or both or with cyst aspiration and instillation of a scolicidal agent.

Etiology

Echinococcus granulosus is common in sheep-raising areas of the Mediterranean, Middle East, Australia, New Zealand, South Africa, and South America. It requires canines as definitive hosts and herbivores (eg, sheep, horses, deer) or humans as intermediate hosts. Foci also exist in regions of Canada, Alaska, and California.

E. multilocularis worms are present in foxes, and the hydatid larvae occur in small wild rodents. Infected dogs and other canines are the main link to occasional human infection. *E. multilocularis* occurs mainly in Central Europe, Alaska, Canada, and Siberia. Its range of natural infection in the continental US extends from Wyoming and the Dakotas to the upper Midwest. Rarely, *E. vogelii* or *E. oliganthus* causes polycystic hydatid disease in humans, primarily in the liver.

Pathophysiology

Ingested eggs from animal feces (which may be present in the fur of dogs or other animals) hatch in the gut. Larvae penetrate the intestinal wall, migrate via the circulation, and lodge in the liver or lungs or, less frequently, in the brain, bone, or other organs.

E. granulosus larvae develop slowly (usually over many years) into large unilocular, fluid-filled lesions —hydatid cysts. Brood capsules containing numerous small infective protoscolices form within these cysts. Large cysts may contain > 1 L of highly antigenic hydatid fluid as well as millions of protoscolices. Daughter cysts sometimes form in or outside primary cysts. If a cyst in the liver leaks or ruptures, infection can spread to the peritoneum.

E. multilocularis produces spongy masses that are locally invasive and difficult or impossible to treat surgically. Cysts occur primarily in the liver but can occur in the lungs, or other tissues.

Symptoms and Signs

Although many infections are acquired during childhood, clinical signs may not appear for years, except when cysts are in vital organs. Symptoms and signs may resemble those of a space-occupying tumor.

Liver cysts eventually cause abdominal pain or a palpable mass. Jaundice may occur if the bile duct is obstructed. Rupture into the bile duct, peritoneal cavity, or lung may cause fever, urticaria, or a serious anaphylactic reaction.

Pulmonary cysts can rupture, causing cough, chest pain, and hemoptysis.

Diagnosis

• Imaging

• Serologic testing

• Examination of cyst fluid

Pulmonary cysts are usually discovered on routine chest x-ray as round, often irregular pulmonary masses.

CT, MRI, and ultrasound findings may be pathognomonic if daughter cysts and hydatid sand

(protoscolices and debris) are present, but simple hydatid cysts may be difficult to differentiate from simple benign cysts, abscesses, or benign or malignant tumors. The presence of hydatid sand in aspirated cyst fluid is diagnostic.

Serologic tests (enzyme immunoassay, immunofluorescent assay, indirect hemagglutination assay) are variably sensitive but are useful if positive and should be done. CBC may detect eosinophilia.

Treatment

• Surgical removal or aspiration followed by instillation of a scolicidal agent

• Sometimes albendazole

Surgery, sometimes via laparoscopy, can be curative. Albendazole is often given before surgery to prevent metastatic infections that can occur if cyst contents spill during the procedure. In some centers, percutaneous aspiration under CT guidance is done, followed by instillation of a scolicidal agent (eg, hypertonic saline) and reaspiration (PAIR [percutaneous aspiration-injection-reaspiration]).

For *E. granulosis*, albendazole 400 mg po bid for 1 to 6 mo (7.5 mg/kg bid in children up to a maximum of 400 mg bid) is curative in 30 to 40% of patients and can be used to suppress growth in inoperable cases.

Prognosis for patients with *E. multilocularis* infection is poor unless the entire larval mass can be removed. Surgery is indicated if it is feasible, which depends on the size, location, and manifestations of the lesion. Albendazole in the above doses can suppress growth of inoperable lesions. Liver transplantation has been lifesaving in a few patients.

Hymenolepis nana Infection

(Dwarf Tapeworm Infection)

Hymenolepis nana, a tiny intestinal tapeworm, is the most common human cestode; infection is treated with praziquantel.

Hymenolepis nana is only 15 to 40 mm long. It requires only one host but can also cycle through two. Its larvae migrate only within the gut wall, and its life span is relatively short (4 to 6 wk). *H. nana* is more frequent in populations living in conditions of poverty and poor hygiene, particularly when fleas are present.

H. nana has 3 modes of infection:

• **Indirect 2-host cycle:** Rodents are the primary definitive hosts, and grain beetles, fleas, or other insects feed on contaminated rodent droppings as intermediate hosts; humans can become infected by ingesting parasitized insects.

• **Human-to-human oral-anal cycle:** Eggs are passed from one human to another or recycle externally in a single host.

• **Internal autoinfection:** Eggs hatch within the gut and initiate a 2nd generation without ever exiting the host. Autoinfection can result in massive numbers of worms, which can cause nausea, vomiting, diarrhea, abdominal pain, weight loss, and nonspecific systemic symptoms.

The pronounced cellular and humoral response to the tissue phase of *H. nana* infection probably provides some protection for adult humans living in endemic areas.

Diagnosis is made by finding eggs in stool samples.

Treatment

Praziquantel 25 mg/kg po once is the treatment of choice.

Hymenolepis diminuta Infection

Hymenolepis diminuta can cause intestinal infection.

Hymenolepis diminuta, the rat tapeworm, has a life cycle similar to the indirect cycle of *H. nana*, involving grain insects. *H. diminuta* rarely infects humans but can cause mild diarrhea.

Diagnosis is by finding characteristic eggs in stool.

Infection is effectively treated with praziquantel 25 mg/kg po once.

Coenurosis (*Taenia multiceps* or *T. serialis* Infection)

Taenia multiceps and T. serialis, rare causes of human infection, are acquired by accidental ingestion of eggs from dog feces.

Canines are the definitive hosts for adult *Taenia multiceps* and *T. serialis* tapeworms; sheep and other herbivorous animals are intermediate hosts. Unwitting ingestion of material contaminated by dog feces causes human disease. The larvae invade and form a cyst (coenurus) in human tissue, usually in the CNS.

Symptoms require several years to develop and depend on the organ infected. Involvement of the brain causes increased intracranial pressure, seizures, loss of consciousness, and focal neurologic deficits.

Diagnosis is typically made after surgical removal, which is also the primary treatment. Surgery is typically done for symptomatic, space-occupying lesions.

Sparganosis

Sparganosis is infection with larvae of the tapeworm *Spirometra mansoni* and related species.

Spirometra mansoni affects dogs, cats, and other carnivores. Eggs are passed into freshwater where they are ingested by copepods (eg, *Cyclops*). Frogs, reptiles, and various small mammals ingest them and serve as intermediate hosts. Humans can become infected by accidental ingestion of copepods from water contaminated by cat or dog feces, ingestion of inadequately cooked flesh from another intermediate host, or contact with poultices containing flesh from these sources. In humans, larvae typically migrate to subcutaneous tissue or muscle and form slowly growing masses. Other sites, including the CNS, may be involved but are much less common. Symptoms are caused by mass effect.

Diagnosis is typically made after surgical removal, although it may be suggested when imaging detects a mass. Surgery is also the primary treatment and is typically done for symptomatic, space-occupying lesions.

Taeniasis saginata

(Beef Tapeworm Infection)

Infection with the beef tapeworm, *Taenia saginata*, may cause mild GI upset or passage of a motile segment in the stool. It is treated with praziquantel.

Cattle are intermediate hosts for *Taenia saginata*. Humans are infected by eating cysticerci (larval form) in raw or undercooked beef. The larvae mature in about 2 mo to adult worms that can live for several years; usually, only 1 or 2 adult worms are present.

Infection occurs worldwide but especially in cattle-raising regions of the tropics and subtropics in Africa, the Middle East, Eastern Europe, Mexico, and South America. Infection is uncommon in US cattle and is

monitored by federal inspection.

Patients may be asymptomatic or have mild digestive symptoms. Passage of a motile segment often brings an otherwise asymptomatic patient to medical attention.

The stool should be examined for proglottids and eggs; eggs may also be present on anal swabs. The ova of *T. saginata* are indistinguishable from those of *T. solium* (pork tapeworm), as are the clinical features and management of intestinal infections due to the 2 tapeworms.

Treatment

• Praziquantel or niclosamide

Treatment is with a single oral dose of praziquantel 5 or 10 mg/kg. Alternatively, a single 2-g dose of niclosamide is given as 4 tablets (500 mg each) that are chewed one at a time and swallowed with a small amount of water. For children, the dose is 40 to 50 mg/kg once. Both drugs have cure rates of about 90%. Treatment can be considered successful when no proglottids are passed for 4 mo.

Taeniasis Solium and Cysticercosis

(Pork Tapeworm Infection)

Taeniasis solium is infection with adult T*aenia solium* worms that follows ingestion of contaminated pork, resulting in intestinal infection. Cysticercosis is infection with larvae of *T. solium*, which develop from ova excreted with human feces. Adult worms may cause mild GI symptoms or passage of a motile segment in the stool. Cysticercosis is usually asymptomatic unless larvae invade the CNS, resulting in neurocysticercosis, which can cause seizures and various other neurologic signs. Neurocysticercosis may be recognized on brain imaging studies. Less than half of patients with neurocysticercosis have adult *T. solium* in their intestines and thus eggs or proglottids in their stool. Adult worms can be eradicated with praziquantel. Treatment of symptomatic neurocysticercosis is with corticosteroids, anticonvulsants, and, in some situations, albendazole or praziquantel. Surgery may be required.

Presentation, diagnosis, and management of intestinal infection with the adult *T. solium* tapeworm are similar to those of beef tapeworm infection. However, humans may also act as intermediate hosts for *T. solium* larvae if they ingest *T. solium* eggs from human excreta (see Fig. 146-1). Another theory is that if an adult tapeworm is present in the intestine, gravid proglottids may be passed retrograde from the intestine to the stomach, where oncospheres (immature form of the parasite enclosed in an embryonic envelope) may hatch and migrate to subcutaneous tissue, muscle, viscera, and the CNS.

Adult tapeworms may reside in the small bowel for years. They may be 2 to 7 m long and produce < 1000 proglottids; each contains about 50,000 eggs.

Cysticercosis is prevalent, and neurocysticercosis is a major cause of seizure disorders in Latin America, Africa, Southeast Asia, and Eastern Europe. Infection in the US is most common among immigrants from those areas but has occurred in North Americans who have not traveled abroad but who have apparently been infected through exposure to immigrants harboring adult *T. solium*.

Symptoms and Signs

Humans infected with adult *T. solium* worms are asymptomatic or have mild GI complaints.

Cysticercosis: Viable cysticerci (larval form) in most organs cause minimal or no tissue reaction, but death of the cysts in the CNS can elicit an intense tissue response. Thus, symptoms often do not appear for years after infection. Infection in the brain (cerebral cysticercosis) may result in severe symptoms, resulting from mass effect and inflammation induced by degeneration of cysticerci and release of antigens.

Patients may present with seizures, signs of increased intracranial pressure, hydrocephalus, focal neurologic signs, altered mental status, or aseptic meningitis. Cysticerci may also infect the spinal cord, muscles, subcutaneous tissues, and eyes. Substantial secondary immunity develops after larval infection.

Diagnosis

• Microscopic examination of stool

• Imaging and serologic testing for patients with CNS symptoms

T. solium eggs are present in ≤ 50% of stool samples from patients with cysticercosis. Diagnosis is usually made when CT or MRI is done to evaluate neurologic symptoms. Scans may show solid nodules, cysts, calcified cysts, ring-enhancing lesions, or hydrocephalus. The CDC's (Centers for Disease Control and Prevention's) immunoblot assay (using a serum specimen) is highly specific and more sensitive than other enzyme immunoassays (particularly when > 2 CNS lesions are present; sensitivity is lower when only a single cyst is present). Infection with adult *T. solium* worms can usually be diagnosed using stool samples.

Treatment

• **For intestinal infection:** Praziquantel

• **For cysticercosis:** Corticosteroids, anticonvulsants, and sometimes surgery

Intestinal infection is treated with praziquantel 5 to 10 mg/kg po as a single dose to eliminate adult worms.

Corticosteroids (prednisone 60 mg po once/day or dexamethasone 6 mg once/day) and anticonvulsants should be given to patients with symptomatic neurocysticercosis to reduce inflammation and symptoms.

The anthelmintic treatment of choice for cerebral cysticercosis is controversial. Not all patients respond to treatment, and not all patients must be treated (cysts may already be dead and calcified, or the inflammatory response to treatment may be worse than the disease). When anthelmintic treatment is used, albendazole 400 mg po bid for 8 to 30 days is the drug of choice; praziquantel 33.3 mg/kg po tid on day 1 followed by 16.6 mg/kg po tid for 29 days can also be used. Neither albendazole nor praziquantel should be used in patients with ocular or spinal cord involvement.

Surgery may be necessary for obstructive hydrocephalus (due to intraventricular cysticerci), infection of the 4th ventricle, and spinal and ocular cysticercosis.

[**Fig. 146-1.** *Taenia solium* life cycle.]

Chapter 147. Intestinal Protozoa

Introduction

The most important intestinal protozoan pathogens are *Entamoeba histolytica, Cryptosporidium* sp, *Giardia intestinalis* (*lamblia*), *Cystoisospora* (*Isospora*) *belli*, *Cyclospora cayetanensis*, and members of the phylum Microsporidia. Multiple pathogenic parasites and nonpathogenic commensal organisms may be present in the intestine at the same time. Nonintestinal protozoan infections are covered in other chapters: For systemic protozoal diseases (malaria, babesiosis, leishmaniasis, toxoplasmosis, trypanosomiasis), see p. ; for nematode infections, see p. ; for fluke infections, see p. ; and for tapeworm infections, see p. .

Intestinal protozoa are spread by the fecal-oral route, so infections are widespread in areas with inadequate sanitation and water treatment. They are also common in the US in settings where fecal incontinence and poor hygiene prevail, as occur in mental institutions and day care centers. Occasionally, large waterborne outbreaks of intestinal protozoan infection have occurred in the US (eg, the massive waterborne *Cryptosporidium* outbreak in Milwaukee in 1993). Some GI protozoa are spread sexually, especially with practices involving oral-anal contact, and several protozoan species cause severe opportunistic infections in patients with AIDS.

Diagnosis

Making a diagnosis based on symptoms and physical findings is difficult; stool testing for parasite antigens or microscopic examination of stool for cysts or organisms is necessary.

Fecal antigen tests that are sensitive and specific are available for

• *G. intestinalis*

• *Cryptosporidium* sp

• *E. histolytica*

Microscopic diagnosis may require several samples, concentration methods, and special stains; thus, the laboratory should be notified which pathogen or pathogens are suspected. Some patients require semi-invasive diagnostic techniques such as endoscopic biopsy (see Table 143-1 on p.).

Amebiasis

(Entamebiasis)

Amebiasis is infection with *Entamoeba histolytica*. It is commonly asymptomatic, but symptoms ranging from mild diarrhea to severe dysentery may occur. Extraintestinal infections include liver abscesses. Diagnosis is by identifying *E. histolytica* in stool specimens or by serologic tests. Treatment for symptomatic disease is with metronidazole or tinidazole followed by paromomycin or other drugs active against cysts in the lumen.

Three species of *Entamoeba* are morphologically indistinguishable, but molecular techniques show that they are different species:

• *E. histolytica* (pathogenic)

• *E. dispar* (harmless colonizer, more common)

• *E. moshkovskii* (harmless colonizer)

Disease is caused by *E. histolytica* and tends to occur in regions with poor socioeconomic conditions and poor sanitation. Most infections occur in Central America, western South America, western and southern Africa, and the Indian subcontinent. In developed countries (eg, US), most cases occur among recent immigrants and travelers returning from endemic regions.

Worldwide each year, an estimated 40 to 50 million people develop amebic colitis or extraintestinal disease, and about 40,000 to 70,000 die.

Pathophysiology

Entamoeba sp exist in 2 forms:

• Trophozoite

• Cyst

The motile trophozoites feed on bacteria and tissue, reproduce, colonize the lumen and the mucosa of the large intestine, and sometimes invade tissues and organs. Trophozoites predominate in liquid stools but rapidly die outside the body. Some trophozoites in the colonic lumen become cysts that are excreted with stool.

Cysts predominate in formed stools and resist destruction in the external environment. They may spread directly from person to person or indirectly via food or water. Amebiasis can also be sexually transmitted by oral-anal contact.

E. histolytica trophozoites can adhere to and kill colonic epithelial cells and PMNs and can cause dysentery with blood and mucus but with few PMNs in stool. Trophozoites also secrete proteases that degrade the extracellular matrix and permit invasion into the intestinal wall and beyond. Trophozoites can spread via the portal circulation and cause necrotic liver abscesses. Infection may spread by direct extension from the liver to the right lung and pleural space or, rarely, through the bloodstream to the brain and other organs.

Symptoms and Signs

Most infected people are asymptomatic but chronically pass cysts in stools. Symptoms that occur with tissue invasion include intermittent diarrhea and constipation, flatulence, and cramping abdominal pain. Tenderness over the liver or ascending colon may occur, and stools may contain mucus and blood.

Amebic dysentery: This form, common in the tropics, manifests with episodes of frequent semiliquid stools that often contain blood, mucus, and live trophozoites. Abdominal findings range from mild tenderness to frank abdominal pain, with high fevers and toxic systemic symptoms. Abdominal tenderness frequently accompanies amebic colitis. Between relapses, symptoms diminish to recurrent cramps and loose or very soft stools, but emaciation and anemia may develop. Symptoms suggesting appendicitis may occur. Surgery in such cases may result in peritoneal spread of amebas.

Chronic amebic infection: This infection can mimic inflammatory bowel disease and manifests as intermittent nondysenteric diarrhea with abdominal pain, mucus, flatulence, and weight loss. Chronic infection may also manifest as tender, palpable masses or annular lesions (amebomas) in the cecum and ascending colon.

Extraintestinal amebic disease: Extraintestinal disease originates from infection in the colon and can involve any organ, but a liver abscess, usually single and in the right lobe, is the most common. It can manifest in patients who had no prior symptoms, is more common among men than among women (7:1 to 9:1), and may develop insidiously.

Symptoms include pain or discomfort over the liver, which is occasionally referred to the right shoulder, as well as intermittent fever, sweats, chills, nausea, vomiting, weakness, and weight loss. Jaundice is unusual and low grade when present. The abscess may perforate into the subphrenic space, right pleural

cavity, right lung, or other adjacent organs (eg, pericardium).

Skin lesions are occasionally observed, especially around the perineum and buttocks in chronic infection, and may also occur in traumatic or operative wounds.

Diagnosis

• **Intestinal infection:** Microscopic examination and, when available, enzyme immunoassay of stool

• **Extraintestinal infection:** Imaging and serologic testing or a therapeutic trial

Nondysenteric amebiasis may be misdiagnosed as irritable bowel syndrome, regional enteritis, or diverticulitis. A right-sided colonic mass may also be mistaken for cancer, TB, actinomycosis, or lymphoma.

Amebic dysentery may be confused with shigellosis, salmonellosis, schistosomiasis, or ulcerative colitis. In amebic dysentery, stools are usually less frequent and watery than those in bacillary dysentery. They characteristically contain tenacious mucus and flecks of blood. Unlike stools in shigellosis, salmonellosis, and ulcerative colitis, amebic stools do not contain large numbers of WBCs because trophozoites lyse them.

Hepatic amebiasis and amebic abscess must be differentiated from other hepatic infections and tumors.

Diagnosis of amebiasis is supported by finding amebic trophozoites, cysts, or both in stool or tissues; however, pathogenic *E. histolytica* are morphologically indistinguishable from nonpathogenic *E. dispar* and *E. moshkovskii*.

Intestinal infection: Identification of intestinal amebas may require examination of 3 to 6 stool specimens and concentration methods (see Table 143-1 on p. 1337). Antibiotics, antacids, antidiarrheals, enemas, and intestinal radiocontrast agents can interfere with recovery of the parasite and should not be given until the stool has been examined. *E. histolytica* also has to be distinguished from nonpathogenic amebas such as *E coli, E. hartmanni, Endolimax nana*, and *Iodamoeba butschlii*.

In symptomatic patients, proctoscopy often shows characteristic flask-shaped mucosal lesions, which should be aspirated, and the aspirate should be examined for trophozoites. Biopsy specimens from rectosigmoid lesions may also show trophozoites.

Extraintestinal infection: This infection is more difficult to diagnose. Stool examination is usually negative, and recovery of trophozoites from aspirated pus is uncommon. If a liver abscess is suspected, ultrasonography, CT, or MRI should be done. They have similar sensitivity; however, no technique can differentiate amebic from pyogenic abscess with certainty.

Needle aspiration is reserved for lesions of uncertain etiology, those in which rupture seems imminent, and those that respond poorly to drug therapy. Abscesses contain thick, semifluid material ranging from yellow to chocolate-brown. A needle biopsy may show necrotic tissue, but motile amebas are difficult to find in abscess material, and amebic cysts are not present.

A therapeutic trial of an amebicide is often the most helpful diagnostic tool for an amebic liver abscess.

Serologic tests are positive in about 95% of patients with an amebic liver abscess, in > 70% of those with active intestinal infection, and in 10% of asymptomatic carriers. Enzyme immunoassay (EIA) is the most widely used. Antibody titers can confirm *E. histolytica* infection but may persist for months or years, making it impossible to differentiate acute from past infection in residents from areas with a high prevalence of infection. *E. histolytica, E. dispar*, and *E. moshkovskii* are morphologically indistinguishable, so microscopic examination cannot be used to differentiate them. A sensitive and specific antigen detection assay for the *E. histolytica* adherence lectin has been developed and is available. PCR-based assays are available in research settings.

Treatment

• Metronidazole or tinidazole initially

• Iodoquinol, paromomycin, or diloxanide furoate subsequently for cyst eradication

For **mild to moderate GI symptoms**, oral metronidazole 500 to 750 mg tid in adults (12 to 17 mg/kg tid in children) for 7 to 10 days is recommended. Metronidazole should not be given to pregnant women. Alcohol must be avoided because of the drug's disulfiram-like effect. Alternatively, tinidazole 2 g po once/day in adults (50 mg/kg [maximum 2 g] po once/day in children > 3 yr) for 3 days can be used. When taken with alcohol, tinidazole also has a disulfiram-like effect, and it should not be used during pregnancy; however, in terms of GI adverse effects, it is generally better tolerated than metronidazole.

For **severe intestinal and extraintestinal amebiasis**, metronidazole 750 mg tid in adults (12 to 17 mg/kg tid in children) for 7 to 10 days is used. Alternatively, tinidazole 2 g po once/day in adults (50 mg/kg [maximum 2 g] po once/day in children > 3 yr) for 5 days can be used.

A course of metronidazole or tinidazole should be followed by a 2nd oral drug to eradicate residual cysts in the lumen. Options are

• Iodoquinol 650 mg po tid in adults (10 to 13 mg/kg [maximum of 2 g/day] tid in children) for 20 days

• Paromomycin 8 to 11 mg/kg tid for 7 days

• Diloxanide furoate 500 mg po tid in adults (7 mg/kg po tid in children) for 10 days

Diloxanide furoate is not available commercially in the US.

Therapy should include rehydration with fluid and electrolytes and other supportive measures.

Asymptomatic people who pass *E. histolytica* cysts should be treated with paromomycin, iodoquinol, or diloxanide furoate (see above for doses). Although metronidazole and tinidazole have some activity against *E. histolytica* cysts, it is not sufficient for them to be used for cyst eradication.

Treatment is not necessary for *E. dispar* or *E. moshkovskii* infections. However, if fecal antigen testing to differentiate them from *E. histolytica* is not available, the decision to treat is made clinically (eg, by the likelihood of exposure to *E. histolytica*).

Prevention

Contamination of food and water with human feces must be prevented—a problem complicated by the high incidence of asymptomatic carriers. Uncooked foods, including salads and vegetables, and potentially contaminated water and ice should be avoided in developing areas. Boiling water kills *E. histolytica* cysts. The effectiveness of chemical disinfection with iodine- or chlorine-containing compounds depends on the temperature of the water and amount of organic debris in it. Portable filters provide various degrees of protection.

Work continues on the development of a vaccine, but none is available yet.

Cryptosporidiosis

Cryptosporidiosis is infection with *Cryptosporidium*. The primary symptom is watery diarrhea, often with other signs of GI distress. Illness is typically self-limited in immunocompetent patients but can be persistent and severe in patients with AIDS. Diagnosis is by identification of the organism or antigen in stool. Treatment, when necessary, is with nitazoxanide.

Pathophysiology

Cryptosporidia are coccidian protozoa that replicate in small-bowel epithelial cells of a vertebrate host. Infective oocysts are shed into the lumen and passed in stool. Very few oocysts (eg, < 100) are required to cause disease, thus increasing risk of person-to-person transmission. After ingestion by another vertebrate, the oocyst releases sporozoites that transform into trophozoites in epithelial cells, replicate, and then produce oocysts that are released into the lumen of the intestine to complete the cycle. Thin-walled oocysts are involved in autoinfection.

Oocysts are resistant to harsh conditions, including chlorine at levels usually used in public water treatment systems.

Epidemiology

Cryptosporidium parvum and *C. hominis* are responsible for most human cases. Infections result from fecally contaminated food or water, direct person-to-person contact, or zoonotic spread. The disease occurs worldwide. Cryptosporidiosis is responsible for 0.6 to 7.3% of diarrheal illness in developed countries and an even higher percentage in areas with poor sanitation. In Milwaukee, Wisconsin, > 400,000 people were affected during a waterborne outbreak in 1993, when the city's water supply was contaminated by run-off from dairy farms during spring rains and the filtration system was not working correctly.

Children, travelers to foreign countries, immunocompromised patients, and medical personnel caring for patients with cryptosporidiosis are at increased risk. Outbreaks have occurred in day care centers. Severe, chronic diarrhea due to cryptosporidiosis is a problem in patients with AIDS.

Symptoms and Signs

The incubation period is about 1 wk, and clinical illness occurs in > 80% of infected people. Onset is abrupt, with profuse watery diarrhea, abdominal cramping, and, less commonly, nausea, anorexia, fever, and malaise. Symptoms usually persist 1 to 2 wk, rarely ≥ 1 mo, and then abate. Fecal excretion of oocysts may continue for several weeks after symptoms have subsided. Asymptomatic shedding of oocysts is common among older children in developing countries.

In the immunocompromised host, onset may be more gradual, but diarrhea can be more severe. Unless the underlying immune defect is corrected, infection can persist, causing profuse intractable diarrhea for life. Fluid losses of > 5 to 10 L/day have been reported in some AIDS patients. The intestine is the most common site of infection in immunocompromised hosts; however, other organs (eg, biliary tract, pancreas, respiratory tract) may be involved.

Diagnosis

• Microscopic examination of stool (special techniques required)

• Enzyme immunoassay for fecal antigen

Identifying the acid-fast oocysts in stool confirms the diagnosis, but conventional methods of stool examination are unreliable. Oocyst excretion is intermittent, and multiple stool samples may be needed. Several concentration techniques increase the yield. *Cryptosporidium* oocysts can be identified by phase-contrast microscopy or by staining with modified Ziehl-Neelsen or Kinyoun techniques. Immunofluorescence microscopy with fluorescein-labeled monoclonal antibodies allows for greater sensitivity and specificity.

Enzyme immunoassay for fecal *Cryptosporidium* antigen is more sensitive than microscopic examination for oocysts. Intestinal biopsy can demonstrate *Cryptosporidium* within epithelial cells.

Treatment

• Nitazoxanide in patients without AIDS

• Highly active antiretroviral therapy (HAART) in patients with AIDS

In immunocompetent people, cryptosporidiosis is self-limited. Nitazoxanide can be used; the recommended doses, given for 3 days, are

• Age 1 to 3 yr: 100 mg bid

• Age 4 to 11 yr: 200 mg bid

• Age > 12 yr: 500 mg bid

No drug has proved to be effective against *Cryptosporidium* in patients with advanced AIDS. Symptoms have abated after effective HAART in some AIDS patients. Supportive measures, oral and parenteral rehydration, and hyperalimentation are indicated for immunocompromised patients.

Prevention

Stools of patients with cryptosporidiosis are highly infectious; strict stool precautions should be observed. Special biosafety guidelines have been developed for handling clinical specimens. Boiling water is the most reliable decontamination method; only filters with pore sizes ≤ 1 μm (specified as "absolute 1 micron" or certified by NSF Standard No. 53) remove *Cryptosporidium* cysts.

Cystoisosporiasis and Cyclosporiasis

Cystoisosporiasis is infection with *Cystoisospora (Isospora) belli*; cyclosporiasis is infection with *Cyclospora cayetanensis*. Both organisms are coccidian protozoa. Symptoms include watery diarrhea with GI and systemic symptoms. Diagnosis is by detection of characteristic oocysts in stool or intestinal biopsy specimens. Treatment is usually with trimethoprim/sulfamethoxazole.

The life cycles of *Cystoisospora belli* and *Cyclospora cayetanensis* are similar to that of *Cryptosporidium*, except that oocysts must sporulate before becoming infective. Human cystoisosporiasis and cyclosporiasis are most common in tropical and subtropical climates. Transmission is by the fecal-oral route via contaminated food or drink. In North America, outbreaks of *C. cayetanensis* have been caused by ingestion of raspberries imported from Guatemala.

Symptoms and Signs

The primary symptom is sudden, nonbloody, watery diarrhea, with fever, abdominal cramps, nausea, anorexia, malaise, and weight loss. In immunocompetent patients, the illness usually resolves spontaneously but can last weeks.

In hosts with depressed cell-mediated immunity as occurs in AIDS, cystoisosporiasis and cyclosporiasis may cause severe, intractable, voluminous diarrhea resembling cryptosporidiosis. Extraintestinal disease in patients with AIDS may include cholecystitis and disseminated infection.

Diagnosis

• Microscopic examination of stool

Diagnosis is by detection of oocysts via microscopic examination of the stool. Detection is facilitated by staining stool samples with modified acid-fast stain. Multiple stool specimens may be needed because cyst secretion may be intermittent. Diagnosis is sometimes made only when intracellular parasite stages are detected in biopsies of intestinal tissue. In cystoisosporiasis, cysts autofluoresce when ultraviolet microscopy is used; the stool may contain Charcot-Leyden crystals (hexagonal, double-pointed, and often needlelike crystals) derived from eosinophils. Unlike other protozoan infections, cystoisosporiasis may result in peripheral blood eosinophilia.

Treatment

• Trimethoprim/sulfamethoxazole

Treatment of choice for both cystoisosporiasis and cyclosporiasis is double-strength trimethoprim/sulfamethoxazole (TMP/SMX): 160 mg TMP and 800 mg SMX po bid for 10 days for cystoisosporiasis or for 7 to 10 days for cyclosporiasis. Children are given 5 mg/kg TMP (and 25 mg/kg SMX) po bid for the same number of days.

In patients with AIDS, higher doses and longer duration may be needed, and treatment of acute infection is usually followed by long-term suppressive therapy.

Ciprofloxacin 500 mg po bid for 7 days has also been used to treat cystoisosporiasis and cyclosporiasis but appears to be less effective than TMP/SMX.

Prevention is as for cryptosporidiosis.

Giardiasis

Giardiasis is infection with the flagellated protozoan *Giardia intestinalis (lamblia)*. Infection can be asymptomatic or cause symptoms ranging from intermittent flatulence to chronic malabsorption. Diagnosis is by identifying the organism in fresh stool or duodenal contents or by assays of *Giardia* antigen in stool. Treatment is with metronidazole, tinidazole, or nitazoxanide or, during pregnancy, paromomycin.

Giardia trophozoites firmly attach to the duodenal and proximal jejunal mucosa and multiply by binary fission. Some organisms transform into environmentally resistant cysts that are spread by the fecal-oral route. Waterborne transmission is the major source of giardiasis. Transmission can also occur by ingestion of contaminated food and by direct person-to-person contact, especially in mental institutions and day care centers or between sex partners. *Giardia* cysts remain viable in surface water and are resistant to routine levels of chlorination. Wild animals may also serve as reservoirs. Thus, mountain streams as well as chlorinated but poorly filtered municipal water supply systems have been implicated in waterborne epidemics.

Symptoms and Signs

Many cases are asymptomatic. However, asymptomatic people can pass infective cysts.

Symptoms of acute giardiasis usually appear 1 to 2 wk after infection. They are usually mild and include watery malodorous diarrhea, abdominal cramps and distention, flatulence, eructation, intermittent nausea, epigastric discomfort, and sometimes low-grade malaise and anorexia. Acute giardiasis usually lasts 1 to 3 wk. Malabsorption of fat and sugars can lead to significant weight loss in severe cases. Neither blood nor WBCs are present in stool.

A subset of infected patients develop chronic diarrhea with foul stools, abdominal distention, and malodorous flatus. Substantial weight loss may occur. Chronic giardiasis occasionally causes failure to thrive in children.

Diagnosis

• Enzyme immunoassay for antigen in stool

• Microscopic examination of stool

Enzyme immunoassay to detect parasite antigen in stool is more sensitive than microscopic examination. Characteristic trophozoites or cysts in stool are diagnostic, but parasite excretion is intermittent and at low levels during chronic infections. Thus, microscopic diagnosis may require repeated stool examinations. Sampling of the upper intestinal contents can also yield trophozoites but is seldom necessary. Specific

DNA probes are under evaluation.

Treatment

• Tinidazole, metronidazole, or nitazoxanide

For symptomatic infections, metronidazole 250 mg po tid in adults (5 mg/kg po tid in children) for 5 to 7 days can be used. Adverse effects include nausea, headaches, and a disulfiram-like effect if alcohol is consumed concurrently. Tinidazole 2 g once in adults (50 mg/kg [maximum 2 g] in children) is as effective as and less toxic than metronidazole. Neither of these drugs should be taken with alcohol.

Nitazoxanide is given orally for 3 days as follows: age 1 to 3 yr, 100 mg bid; age 4 to 11 yr, 200 mg bid; and age > 12 yr (including adults), 500 mg bid. It is available in liquid form for children.

Furazolidone and quinacrine are effective but are now rarely used because of potential toxicity.

Metronidazole and tinidazole should not be given to pregnant women. Nitazoxanide is in pregnancy category B. If therapy cannot be delayed because of symptoms, the nonabsorbable aminoglycoside paromomycin (8 to 11 mg/kg po tid for 5 to 10 days) is an option.

Prevention

Prevention requires appropriate public water treatment, hygienic food preparation, and appropriate fecal-oral hygiene. Water can be decontaminated by boiling. *Giardia* cysts resist routine levels of chlorination. Disinfection with iodine-containing compounds is variably effective and depends on the turbidity and temperature of the water and duration of treatment. Some handheld filtration devices can remove *Giardia* cysts from contaminated water, but the efficacy of various filter systems has not been fully assessed.

Treatment of asymptomatic cyst passers can theoretically reduce the spread of infection, but whether it is cost-effective remains unclear.

Microsporidiosis

Microsporidiosis is infection with microsporidia. Symptomatic disease develops predominantly in patients with AIDS and includes chronic diarrhea, disseminated infection, and corneal disease. Diagnosis is by demonstrating organisms in biopsy specimens, stool, urine, other secretions, or corneal scrapings. Treatment is with albendazole or fumagillin (depending on the infecting species and clinical syndrome), with topical fumagillin added for eye disease.

Microsporidia are obligate intracellular spore-forming protozoan parasites. At least 14 of the > 1200 species are associated with human disease. Spores of the organisms are acquired by ingestion, inhalation, direct contact with the conjunctiva, animal contact, or person-to-person transmission. Inside the host, they harpoon a host cell with their polar tubule or filament and inoculate it with an infective sporoplasm. Intracellularly, the sporoplasm divides and multiplies, producing sporoblasts that mature into spores; the spores can disseminate throughout the body or pass into the environment via respiratory aerosols, stool, or urine. An inflammatory response develops when spores are liberated from host cells.

Little is known about routes of transmission to humans or possible animal reservoirs. Microsporidia probably are a common cause of subclinical or mild self-limited illness in otherwise healthy people, but only a few cases of human infection were reported in the pre-AIDS era.

Microsporidia have emerged as opportunistic pathogens in patients with AIDS and, to a lesser degree, in those with other immunocompromising conditions. *Encephalitozoon bieneusi* and *E.* (formerly *Septata*) *intestinalis* can cause chronic diarrhea in patients with AIDS and CD4+ cell counts of < 100/μL. Microsporidian species can also infect the biliary tract, cornea, muscles, respiratory tract, GU system, and, occasionally, the CNS.

Symptoms and Signs

Clinical illness caused by microsporidia varies with the parasite species and the immune status of the host. In patients with AIDS, various species cause chronic diarrhea, malabsorption, wasting, cholangitis, punctate keratoconjunctivitis, peritonitis, hepatitis, myositis, or sinusitis. Infections of kidneys, gallbladder, and sinuses have occurred. *Vittaforma (Nosema) corneum* and several other species can cause ocular infections ranging from punctuate keratopathy with redness and irritation to severe, vision-threatening stromal keratitis.

Diagnosis

• Light or electron microscopy with special stains

Infecting organisms can be demonstrated in specimens of affected tissue obtained by biopsy or in stool, urine, CSF, sputum, or corneal scrapings. Microsporidia are best seen with special staining techniques. Fluorescence brighteners (fluorochromes) are used to detect spores in tissues and smears. The quick-hot Gram chromotrope technique is the fastest. Immunoassay and PCR-based tests hold promise for the future.

Transmission electron microscopy is currently the most sensitive test and is used for speciation.

Treatment

• For immunocompetent patients: Supportive care

• For immunocompromised patients: Albendazole alone or with topical fumagillin for corneal disease

In immunocompetent patients, microsporidia infections are usually self-limited, and therapy is seldom necessary.

In immunocompromised patients, albendazole (400 mg po bid for 21 days in adults) may be effective in controlling intestinal infection with *E. intestinalis*. The drug reduces the number of organisms in small-bowel biopsies but does not eliminate infection. Fumagillin 20 mg po tid for 14 days has been used for *E. bieneusi*, but it has adverse effects (eg, bone marrow suppression).

Ocular lesions (due to *Brachiola algerae, E. hellem*, or *E. cuniculi*) have been treated with albendazole 400 mg bid plus fumagillin eyedrops. These drugs are also used for *V. corneum*, but they frequently fail, and keratoplasty may be required.

Albendazole 400 mg bid has been used for patients with disseminated disease and skin and deep muscle infection caused by numerous microsporidian species.

Treatment of AIDS with highly active antiretroviral therapy (HAART) is important and can lead to reduction in symptoms.

Chapter 148. Extraintestinal Protozoa

Introduction

Protozoa are motile, single-celled organisms that occur worldwide. Many of those that cause extraintestinal infections are transmitted by arthropod vectors. These infections include African trypanosomiasis, Chagas disease, leishmaniasis, and malaria. Toxoplasmosis is acquired through contaminated food. Free-living amebas are acquired through contact with surface water or soil.

African Trypanosomiasis

(African Sleeping Sickness)

African trypanosomiasis is infection with protozoa of the genus _Trypanosoma_, transmitted by the bite of a tsetse fly. Symptoms include characteristic skin lesions, intermittent fever, headache, rigors, transient edema, generalized lymphadenopathy, and often fatal meningoencephalitis. Diagnosis is by identification of the organism in blood, lymph node aspirate, or CSF or sometimes by serologic tests. Treatment is with suramin, pentamidine, melarsoprol, or eflornithine, depending on the infecting subspecies, clinical stage, and drug availability.

African trypanosomiasis is caused by _Trypanosoma brucei gambiense_ in West and Central Africa and by _T. brucei rhodesiense_ in East Africa; both species are endemic in Uganda. The organisms are transmitted by tsetse flies and occasionally by blood transfusion.

Pathophysiology

Metacyclic trypomastigotes inoculated by flies transform into bloodstream trypomastigotes, which multiply by binary fission and spread through the lymphatics and bloodstream after inoculation. Bloodstream trypomastigotes multiply until specific antibodies produced by the host sharply reduce parasite levels. However, a subset of parasites escape immune destruction by a change in their variant surface glycoprotein and start a new multiplication cycle. The cycle of multiplication and lysis repeats. Late in the course of infection, trypanosomes appear in the interstitial fluid of many organs, including the myocardium and eventually the CNS. The cycle is continued when a tsetse fly bites an infected human. Humans are the main reservoir of _T. b. gambiense_, but this species may also reside in animals. Wild game animals are the main reservoir of _T. b. rhodesiense_.

Symptoms and Signs

The disease has 3 stages:

• Cutaneous

• Hemolymphatic

• CNS

Cutaneous: A papule may develop at the site of the tsetse fly bite within a few days to 2 wk. It evolves into a dusky red, painful, indurated nodule (trypanosomal chancre). A chancre is present in about half of Caucasians with _T. b. rhodesiense_ but is less common in Africans with _T. b. rhodesiense_ and seldom occurs with _T. b. gambiense_.

Hemolymphatic: Over several months in _T. b. gambiense_ infection but a period of weeks with _T. b. rhodesiense_, intermittent fever, headaches, rigors, and transient swellings develop. An evanescent, circinate erythematous rash may develop. It is most readily visible in light-skinned patients. Generalized lymphadenopathy often occurs. Winterbottom's sign (enlarged lymph nodes in the posterior cervical triangle) is characteristic with _T. b. gambiense_ sleeping sickness.

CNS: In the Gambian form, CNS involvement occurs months to several years after onset of acute disease. In the Rhodesian form, disease is more fulminant, and CNS invasion often occurs within a few weeks. CNS involvement causes persistent headache, inability to concentrate, personality changes (eg, progressive lassitude and indifference), daytime somnolence, hyperphagia, tremor, ataxia, and terminal coma. Without treatment, death occurs within months of disease onset with *T. b. rhodesiense* and during the 2nd or 3rd yr with *T. b. gambiense*. Untreated patients die in coma of undernutrition or secondary infections.

Diagnosis

• Light microscopy of blood (thin or thick smears) or other fluid sample

Diagnosis is made by identifying trypanosomes in fluid from a chancre, lymph node aspirate, blood, bone marrow aspirate, or, during the late stage of infection, CSF. Preferred sources are blood smears for *T. b. rhodesiense* and fluid aspirated from an enlarged lymph node for *T. b. gambiense*. Wet preparations should be examined for motile trypanosomes, and smears should be fixed, stained with Giemsa (or Field's) stain, and examined. Concentration techniques (eg, centrifugation of blood or CSF) enhance sensitivity.

Antibody detection assays are not very useful clinically because seroconversion occurs after the onset of symptoms. However, a card agglutination test for *T. b. gambiense* is useful in mass screening programs to identify candidates for microscopic examination.

When the CNS is involved, lumbar puncture is done. CSF pressure is increased, and CSF has elevated levels of lymphocytes (≥ 5 cells/μL), total protein, and IgM. In addition to trypanosomes, characteristic Mott cells (plasma cells with cytoplasmic vacuoles that contain immunoglobulin [Russell bodies]) may be present.

Other, nonspecific laboratory findings include anemia, monocytosis, and markedly elevated serum levels of polyclonal IgM.

Treatment

• Without CNS involvement, pentamidine or eflornithine for *T. b. gambiense*; suramin for *T. b. rhodesiense*

• With CNS involvement, eflornithine or melarsoprol for *T. b. gambiense*; melarsoprol for *T. b. rhodesiense*

Without CNS involvement: Suramin and pentamidine are effective against bloodstream stages of both *T. brucei* subspecies but do not cross the blood-brain barrier and are not useful for CNS infection. Pentamidine is preferred for *T. b. gambiense*, and suramin is preferred for the hemolymphatic stage of *T. b. rhodesiense*. The dosage of pentamidine is 4 mg/kg IM or IV once/day for 7 days. An initial test dose of suramin 100 mg IV (to exclude hypersensitivity) is followed by 20 mg/kg (up to 1 g) IV on days 1, 3, 7, 14, and 21.

Eflornithine (availability limited) is effective against all stages of *T. b. gambiense* (but not *T. b. rhodesiense*) trypanosomiasis. Dosage is 100 mg/kg IV qid for 14 days. When available, it is the drug of choice for *T. b. gambiense*.

With CNS involvement: Melarsoprol, an organic arsenical, is used in most African countries for CNS disease. For *T. b. gambiense*, dosage is 2.2 mg/kg IV once/day for 10 days. Where available, eflornithine can be used in the regimen above for *T. b. gambiense* CNS disease. For *T. b. rhodesiense*, dosage is 2 to 3.6 mg/kg IV once/day for 3 days; after 7 days, 3.6 mg/kg once/day is given for 3 days, followed 7 days later by another 3-day course at this dose. Alternative regimens have been proposed for debilitated patients with severe CNS involvement.

Serious adverse effects include reactive encephalopathy and exfoliative dermatitis in addition to the usual

GI and renal toxicity of arsenicals.

Corticosteroids have been used to decrease the risk of reactive encephalopathy.

Prevention

Prevention includes avoiding endemic areas and protecting against tsetse flies. Visitors to game parks should wear substantial wrist- and ankle-length clothing (tsetse flies bite through thin clothes) and use insect repellents with DEET (diethyltoluamide) appropriately.

Pentamidine can help prevent *T. b. gambiense* infection, but it may damage pancreatic β-cells, resulting in insulin release and hypoglycemia followed later by diabetes; thus, it is seldom used for prophylaxis.

Babesiosis

Babesiosis is infection with *Babesia* sp. Infections can be asymptomatic or cause a malaria-like illness with fever and hemolytic anemia. Disease is most severe in asplenic patients, the elderly, and patients with AIDS. Diagnosis is by identification of *Babesia* in a peripheral blood smear, serologic test, or PCR. Treatment, when needed, is with azithromycin plus atovaquone or with quinine plus clindamycin.

Etiology

In the US, *Babesia microti* is the most common cause of babesiosis. Rodents are the principal natural reservoir, and deer ticks of the family Ixodidae are the usual vectors. Larval ticks become infected while feeding on an infected rodent, then transform into nymphs that transmit the parasite to another animal or to a human. Adult ticks ordinarily feed on deer but may also transmit the parasite to humans. *Babesia* enter RBCs, mature, and then divide asexually. Infected erythrocytes eventually rupture and release organisms that invade other RBCs; thus, *Babesia* can also be transmitted by blood transfusion.

Endemic areas in the US include the islands and the mainland bordering Nantucket Sound in Massachusetts, eastern Long Island and Shelter Island in New York, coastal Connecticut, and New Jersey, as well as foci in Wisconsin and the upper Midwest. *Babesia duncani* has been isolated from patients in Washington and California. A currently unnamed strain designated MO-1 has been reported in patients in Missouri. Other *Babesia* sp transmitted by different ticks infect humans in areas of Europe. In Europe, *B. divergens* is the principle cause of babesiosis in patients who have had a splenectomy.

Ixodes ticks infected with *Babesia* are sometimes coinfected with *Borrelia burgdorferi* (which causes Lyme disease), *Anaplasma phagocytophilum* (which causes human granulocytic anaplasmosis), or both.

Symptoms and Signs

Asymptomatic infection may persist for months to years and remain subclinical throughout its course in otherwise healthy people, especially those < 40 yr.

When symptomatic, the illness usually starts after a 1- to 2-wk incubation period with malaise, fatigue, chills, fever, headache, myalgia, and arthralgia, which may last for weeks. Hepatosplenomegaly with jaundice, mild to moderately severe hemolytic anemia, mild neutropenia, and thrombocytopenia may occur.

Infection is sometimes fatal, particularly in the elderly, asplenic patients, and patients with AIDS. In such patients, babesiosis may resemble falciparum malaria, with high fever, hemolytic anemia, hemoglobinuria, jaundice, and renal failure. Splenectomy may cause previously acquired asymptomatic parasitemia to become symptomatic.

Diagnosis

• Light microscopy of blood smears

Most patients do not remember a tick bite, but they may report a history of travel to an endemic region.

Diagnosis is usually made by finding *Babesia* in blood smears, but differentiation from *Plasmodium* species can be difficult. Tetrad forms (the so-called Maltese cross formation), although not common, are unique to *Babesia* and helpful diagnostically. Serologic and PCR tests are available. Antibody detection by indirect fluorescent antibody (IFA) testing using *B. microti* antigens can be helpful in patients with low-level parasitemia but may be falsely negative in those infected with other *Babesia* sp. PCR-based assays are available in research settings.

Treatment

• Atovaquone plus azithromycin

Asymptomatic patients require no treatment, but therapy is indicated for patients with persistent high fever, rapidly increasing parasitemia, and falling Hct. The combination of atovaquone 750 mg po q 12 h and azithromycin 600 mg po once/day for 7 to 10 days is as effective as traditional therapy with quinine plus clindamycin and has fewer adverse effects. Pediatric dosage is atovaquone 20 mg/kg bid plus azithromycin 12 mg/kg once/day for 7 to 10 days.

Alternatively, quinine 650 mg po tid for 7 days plus clindamycin 600 mg po tid or 1.2 g IV bid for 7 to 10 days can be used. Pediatric dosage is quinine 10 mg/kg po tid plus clindamycin 7 to 14 mg/kg po tid.

Exchange transfusion has been used in hypotensive patients with high parasitemia.

Standard tick precautions (see Sidebar 139-1 on p. 1283) should be taken by all people in endemic areas. Asplenic patients and patients with AIDS should be particularly cautious.

Chagas Disease

(American Trypanosomiasis)

Chagas disease is infection with *Trypanosoma cruzi*, transmitted by Triatominae bug bites. Symptoms begin with a skin lesion or unilateral periorbital edema, then progress to fever, malaise, generalized lymphadenopathy, and hepatosplenomegaly; years later, some patients develop chronic cardiomyopathy, megaesophagus, or mega-colon. Diagnosis is by detecting trypanosomes in peripheral blood or aspirates from infected organs. Antibody tests are sensitive and can be helpful. Treatment is with nifurtimox or benznidazole.

T. cruzi is transmitted by Triatominae (reduviid, kissing, or assassin) bugs.

Pathophysiology

While biting, infected bugs deposit feces containing metacyclic trypomastigotes on the skin. These infective forms enter through the bite wound or penetrate the conjunctivae or mucous membranes. The parasites invade macrophages at the site of entry and transform into amastigotes that multiply by binary fission; the amastigotes develop into trypomastigotes, enter the bloodstream and tissue spaces, and infect other cells. Cells of the reticuloendothelial system, myocardium, muscles, and nervous system are most commonly involved.

Infection can also be transmitted by blood transfusion, organ transplantation, or ingestion of uncooked food or drink (eg, drinks made from sugar cane juice) contaminated by infected reduviid bugs or their feces. Transplacental transmission is also possible.

Etiology

Infected Triatominae bugs are present in North, Central, and South America. More than 20 million people in the Americas are infected with *T. cruzi*, but the prevalence has been decreasing because of control

measures. In some rural parts of South America, Chagas disease has been a leading cause of death. Nonhuman reservoirs include dogs, cats, opossums, rats, and many other animals.

Vector-borne disease is rare in the US, but some Latin American immigrants living in the US are chronically infected. These people are potential sources of transmission by blood transfusion or organ donation.

Symptoms and Signs

Acute infection is followed by a latent (indeterminate) period, which may remain asymptomatic or progress to chronic disease. Immunosuppression may reactivate latent infection, with high parasitemia and a 2nd acute stage, skin lesions, or brain abscesses. Congenital transmission occurs in 1 to 5% of pregnancies and results in abortion, stillbirth, or chronic neonatal disease with high mortality.

Acute: Acute infection in endemic areas usually occurs in childhood and can be asymptomatic. When present, symptoms start 1 to 2 wk after exposure. An indurated, erythematous skin lesion (a chagoma) appears at the site of parasite entry. When the inoculation site is the conjunctiva, unilateral periocular and palpebral edema with conjunctivitis and preauricular lymphadenopathy are collectively called Romana's sign.

Acute Chagas disease is fatal in a small percentage of patients; death results from acute myocarditis with heart failure or meningoencephalitis. In the remainder, symptoms subside without treatment.

Primary acute Chagas disease in immunocompromised patients, such as those with AIDS, may be severe and atypical, with skin lesions and, rarely, brain abscesses.

Chronic: Chronic disease develops in 20 to 40% after a latent phase that may last years or decades. The main effects are

• Cardiac

• GI

Chronic cardiomyopathy leads to flaccid enlargement of all chambers, apical aneurysms, and localized degenerative lesions in the conduction system. Patients may present with heart failure, syncope, sudden death due to heart block or ventricular arrhythmia, or thromboembolism. ECG may show right bundle branch or complete heart block.

GI disease causes symptoms resembling achalasia or Hirschsprung's disease. Chagas megaesophagus manifests as dysphagia and may lead to pulmonary infections caused by aspiration or to severe undernutrition. Mega-colon may result in long periods of obstipation and intestinal volvulus.

Diagnosis

• Light microscopy of blood smears (thin or thick) or another fluid sample

The number of trypanosomes in peripheral blood is large during the acute phase and readily detected by examining thin or thick smears. In contrast, few parasites are present in blood during latent infection or chronic disease. Definitive diagnosis may be made by examining aspirates from organs such as lymph nodes.

Serologic tests including indirect fluorescent antibody (IFA) and enzyme immunoassays (EIA) are sensitive but may yield false-positive results in patients with leishmaniasis or other diseases. Other diagnostic approaches include xenodiagnosis (examination of the intestinal contents of laboratory-raised bugs after they take a blood meal from a patient suspected of having Chagas disease) and detection of PCR-amplified parasite DNA in blood or tissue fluids.

Treatment

• Nifurtimox or benznidazole

• Supportive care

Treatment in the acute stage rapidly reduces parasitemia, shortens the clinical illness, and reduces risk of mortality due to chronic infection.

For indeterminate infections, treatment of children and young adults has been recommended but is not always curative. Treatment of older adults with indeterminate disease is controversial.

Once the signs of chronic Chagas disease appear, antiparasitic drugs are not helpful.

Supportive measures include treatment for heart failure, pacemakers for heart block, antiarrhythmic drugs, cardiac transplantation, esophageal dilation, botulinum toxin injection into the lower esophageal sphincter, and GI tract surgery.

The only effective drugs are

• **Nifurtimox:** For adults, 2 to 2.5 mg/kg po qid for 3 to 4 mo

  For children aged 11 to 16 yr, 3 to 3.75 mg/kg qid for 3 mo

  For children aged 1 to 10 yr, 4 to 5 mg/kg qid for 3 mo

• **Benznidazole:** For adults and children > 12 yr, 2.5 to 3.5 mg/kg po bid for 1 to 3 mo

  For children ≤ 12 yr, 5 mg/kg bid for 1 to 3 mo

Both drugs have substantial toxicity. The long treatment courses are often associated with GI adverse effects, peripheral neuropathy, poor tolerance, and low compliance.

Prevention

Plastering walls and replacing thatched roofs or repeated spraying of houses with residual insecticides (those that have prolonged duration of action) can control Triatominae bugs. Infection in travelers is rare and can be avoided by not sleeping in adobe dwellings or by using bed nets if sleeping in such dwellings is unavoidable.

Blood and organ donors are screened in many endemic areas and, since 2006, in the US to prevent transfusion and organ transplant-related Chagas disease.

Free-Living Amebas

Free-living amebas are protozoa that live independently in soil or water and do not require a human or animal host. They rarely cause disease, in contrast to the parasitic ameba *Entamoeba histolytica*, which is a common cause of intestinal infection (see p.). Pathogenic free-living amebas are of the genera *Naegleria, Acanthamoeba*, and *Balamuthia*.

Three major syndromes occur:

• Primary amebic meningoencephalitis

• Granulomatous amebic encephalitis

• Amebic keratitis

Acanthamoeba can also cause skin lesions.

Primary Amebic Meningoencephalitis

Primary amebic meningoencephalitis is a generally fatal, acute CNS infection caused by *Naegleria fowleri*.

Naegleria fowleri inhabit bodies of warm fresh water worldwide. Swimming in contaminated water exposes nasal mucosa to the organism, which can enter the CNS via olfactory neuroepithelium and the cribriform plate. Most patients are healthy children or young adults.

Symptoms begin within 1 to 2 wk of exposure, sometimes with alteration of smell and taste. Fulminant meningoencephalitis ensues, with headache, meningismus, and mental status change, progressing to death within 10 days, usually due to cerebral herniation. Only a few patients survive.

Diagnosis is suspected based on history of swimming in fresh water, but confirmation is difficult because CT and routine CSF tests, although necessary to exclude other causes, are nonspecific. Wet mount of CSF should be done; it may demonstrate motile amebic trophozoites (which are destroyed by Gram stain techniques).

Optimal treatment is unclear. A reasonable regimen would include amphotericin B (given intravenously, intrathecally, or both) plus azithromycin or clarithromycin, azole antimicrobials (eg, ketoconazole, fluconazole, miconazole), and perhaps rifampin.

Granulomatous Amebic Encephalitis

Granulomatous amebic encephalitis is a generally fatal subacute CNS infection caused by *Acanthamoeba* sp in immunocompromised or debilitated hosts or by *Balamuthia mandrillaris*.

Acanthamoeba sp and *Balamuthia mandrillaris* are present worldwide in water, soil, and dust. Human exposure is common, but infection is rare. *Acanthamoeba* infection of the CNS occurs almost entirely in immunocompromised or otherwise debilitated patients, but *B. mandrillaris* may also infect healthy hosts. The entry portal is thought to be the skin or lower respiratory tract, with subsequent hematogenous dissemination to the CNS.

Onset is insidious, often with focal neurologic manifestations. Mental status change, seizures, and headache are common. *B. mandrillaris* may also cause skin lesions. Survival is highly unlikely (and only in immunocompetent patients); death occurs between 7 and 120 days after onset (average, 39 days).

Diagnosis is often postmortem. CT and routine CSF tests are obtained but are nonspecific. CT may show multiple nonenhancing lucent areas; in CSF, WBC count (predominantly lymphocytes) is elevated, but trophozoites are rarely seen. Visible skin lesions often contain amebas and should be biopsied; if detected, amebas may be cultured and tested for drug sensitivity. Brain biopsy is often positive.

Some patients with *Acanthamoeba* granulomatous encephalitis have responded to drug combinations, which may include pentamidine; sulfadiazine or trimethoprim/sulfamethoxazole; flucytosine; fluconazole, ketoconazole, itraconazole, or voriconazole; amphotericin B; and other drugs. Skin infections caused by *Acanthamoeba* sp are usually treated with the same drugs and surgical debridement.

B. mandrillaris has been treated with a combination of pentamidine, flucytosine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin combined with surgical resection.

Amebic Keratitis

Amebic keratitis is corneal infection with *Acanthamoeba* sp, typically occurring in contact lens wearers.

Acanthamoeba sp can cause chronic and progressively destructive keratitis in normal hosts. The main risk factor (85% of cases) is contact lens use, particularly if lenses are worn while swimming or if unsterile

lens cleaning solution is used. Some infections follow corneal abrasion.

Lesions are typically very painful and produce a foreign body sensation. Initially, lesions have a dendriform appearance resembling herpes simplex keratitis. Later, there are patchy stromal infiltrates and sometimes a characteristic ring-shaped lesion. Anterior uveitis is usually also present. Vision is diminished.

Diagnosis is confirmed by examination of Giemsa- or trichrome-stained corneal scrapings and by culture on special media. Viral culture is done if herpes is considered.

Treatment

• Corneal debridement

• Topical propamidine plus a biguanide

• Perhaps systemic fluconazole or itraconazole

Early, superficial infection responds better to treatment. The encysted stage of the life cycle appears to cause most problems.

Epithelial lesions are debrided, and intensive drug therapy is applied. Topical propamidine isethionate 0.1% plus either polyhexamethylene biguanide or biguanide chlorhexidine drops is frequently the initial choice; for the first 3 days, drugs are given every 1 to 2 h. Other topical drugs that can be used include aminoglycosides, hexamidine diisethionate, miconazole, and neosporin.

Systemic treatment with fluconazole or itraconazole has also been used, particularly in patients with anterior uveitis or involvement of the sclera. Early recognition and treatment have eliminated the need for therapeutic keratoplasty in most instances, but it remains an option when pharmacologic therapy fails. Intensive treatment is required for the first month; it is tapered per clinical response but often continued for 6 to 12 mo. Recurrence is common if treatment is stopped prematurely.

Prevention

Contact lens solution should be kept clean. Nonsterile homemade contact lens solutions should not be used. Wearing contact lenses while swimming or showering should be avoided.

Leishmaniasis

Leishmaniasis is caused by species of *Leishmania*. Manifestations include cutaneous, visceral, and mucocutaneous syndromes. Cutaneous leishmaniasis causes painless chronic skin lesions ranging from nodules to large ulcers that can persist for months to years but eventually heal. Visceral leishmaniasis causes irregular fever, hepatosplenomegaly, pancytopenia, and polyclonal hypergammaglobulinemia with high mortality in untreated patients. Mucosal disease affects nasopharyngeal tissues and can cause gross mutilation of the nose and palate. Diagnosis is by demonstrating parasites in smears or cultures. Treatment is with liposomal amphotericin B, amphotericin B deoxycholate, pentavalent antimony compounds (sodium stibogluconate, meglumine antimonate), or miltefosine, depending on the causative species and clinical syndrome.

Etiology

Leishmaniasis is present in scattered areas worldwide. Human infection is caused by about 20 *Leishmania* sp that are morphologically indistinguishable but can be differentiated by laboratory analysis.

Leishmania promastigotes are transmitted by sand flies (*Phlebotomus* sp, *Lutzomyia* sp) to vertebrate hosts. Vector sand flies are infected by biting infected humans or animals. Animal reservoirs vary with the *Leishmania* sp and location and include canines, rodents, and other animals. In the Indian subcontinent,

humans are the reservoir for *L. donovani*. Rarely, infection is spread by blood transfusion, shared needles, congenitally, or sexually.

Pathophysiology

After infection, promastigotes from the vector are phagocytized by host macrophages; inside these cells, they transform into amastigotes.

The parasites may remain localized in the skin or spread to internal organs or the mucosa of the nasopharynx, resulting in 3 major clinical forms of leishmaniasis:

• Cutaneous

• Visceral

• Mucosal

Cutaneous leishmaniasis is also known as oriental or tropical sore, Delhi or Aleppo boil, uta or chiclero ulcer, or forest yaws. The causative agents are *L. major* and *L. tropica* in southern Europe, Asia, and Africa; *L. mexicana* and related species in Mexico and Central and South America; and *L. braziliensis* and related species in Central and South America. Cases have occurred among US military personnel serving in Iraq and Afghanistan and among travelers to endemic areas in Central and South America, Israel, and elsewhere. Uncommonly, *L. braziliensis* spreads widely in the skin causing disseminated cutaneous leishmaniasis.

Visceral leishmaniasis (kala-azar, Dumdum fever) is typically caused by *L. donovani* or *L. infantum/chagasi* and occurs in India, Africa (particularly the Sudan), Central Asia, the Mediterranean basin, South and Central America, and infrequently China. Most cases occur in northeastern India. Parasites disseminate from the site of the sand fly bite in the skin to regional lymph nodes, the spleen, the liver, and bone marrow and cause symptoms. Subclinical infections are common; only a minority of infected patients develop progressive visceral disease. Symptomatic infection with *L. infantum/chagasi* is more common among children than adults. Visceral leishmaniasis is an opportunistic infection in patients with AIDS or other immunocompromising conditions.

Mucosal leishmaniasis (espundia) is caused mainly by *L. braziliensis*, but it occasionally occurs with other *Leishmania* sp in the Americas. The parasites spread from the initial skin lesion through lymphatics and blood to nasopharyngeal tissues. Symptoms and signs of mucosal disease develop months to years later.

Symptoms and Signs

In **cutaneous leishmaniasis,** a welldemarcated skin lesion develops at the site of a sand fly bite, usually within several weeks to months. Multiple lesions may occur after multiple infective bites or with metastatic spread. The initial lesion is often a papule that slowly enlarges, ulcerates centrally, and develops a raised, erythematous border where intracellular parasites are concentrated. Ulcers are painless and cause no systemic symptoms unless secondarily infected. Lesions typically heal spontaneously after several months but may persist for years. They leave a depressed, burn-like scar. The course depends on the infecting *Leishmania* sp and the host's immune status. Diffuse cutaneous leishmaniasis results in widespread nodular skin lesions resembling those of lepromatous leprosy. It results from cell-mediated anergy to the organism.

In **visceral leishmaniasis,** the clinical manifestations usually develop gradually over weeks to months after inoculation of the parasite. Irregular fever, hepatosplenomegaly, pancytopenia, and polyclonal hypergammaglobulinemia with a reversed albumin:globulin ratio occur. In some patients, there are twice-daily temperature spikes. Emaciation and death occur within months to years in patients with progressive infections. Those with asymptomatic, self-resolving infections and survivors (after successful treatment) are resistant to further attacks unless cell-mediated immunity is impaired (eg, by AIDS). Relapse may occur years after initial infection. After treatment for visceral leishmaniasis, patients in the Sudan and India

may develop post kalaazar dermal leishmaniasis (PKDL) with flat or nodular cutaneous lesions that contain many parasites. These lesions develop at the end of or within 6 mo of therapy in patients in the Sudan and 1 to 2 yr later in India. The lesions persist for a few months to a year in most patients in the Sudan but can last for years in India. PKDL lesions are thought to contribute to the spread of infection.

Mucosal leishmaniasis starts with a primary cutaneous ulcer. This skin lesion heals spontaneously, but months to years later, mucosal lesions develop, sometimes resulting in gross mutilations of the nose, palate, and face.

Diagnosis

• Light microscopy of tissue samples, touch preparations, or aspirates

• For visceral leishmaniasis, antibody titers

• For cutaneous leishmaniasis, sometimes skin testing (not available in the US)

• Culture (special media required)

A definite diagnosis is made by demonstrating organisms in Giemsa-stained smears or cultures of aspirates from the spleen, bone marrow, liver, or lymph nodes in visceral leishmaniasis or biopsy, aspirates, or touch preparations from the border of a cutaneous lesion. Parasites are usually difficult to isolate from mucosal lesions. Organisms causing simple cutaneous leishmaniasis can be differentiated from those capable of causing mucocutaneous leishmaniasis with specific DNA probes or monoclonal antibodies or by analysis of isoenzyme patterns of cultured parasites.

Serologic tests can help diagnose visceral leishmaniasis; high titers of antibodies to a recombinant leishmanial antigen (rk39) are present in most immunocompetent patients with visceral leishmaniasis. Antibodies may be absent in subclinical cases and in patients with cutaneous leishmaniasis or AIDS.

The leishmanin skin test is available outside the US. It is positive in patients with cutaneous and mucosal leishmaniasis but negative in those with active visceral leishmaniasis.

Treatment

• Liposomal amphotericin B

• Pentavalent antimony compounds

• Alternative drugs (eg, amphotericin B deoxycholate, miltefosine, paromomycin)

Supportive measures (eg, adequate nutrition, transfusions, antibiotics for secondary bacterial infection) may be needed for patients with visceral leishmaniasis. Reconstructive surgery may be required if mucocutaneous leishmaniasis grossly distorts the nose or palate, but surgery should be delayed for 6 to 12 mo after therapy to avoid losing grafts because of relapses. This form frequently relapses, as does the visceral form in patients with AIDS. Treatment with highly active antiretroviral therapy (HAART) may reduce risk of relapse.

Drugs are given; selection depends on the form of disease, infecting species, resistance pattern, and geographic location.

Cutaneous leishmaniasis: Parenteral pentavalent antimonials are often used for *Leishmania* sp acquired in regions where resistance is low if the lesion is potentially disfiguring or if the infecting species has the potential to disseminate and cause mucosal leishmaniasis. Drugs include sodium stibogluconate and meglumine antimonite. Doses of both are based on their pentavalent antimony content—20 mg/kg IV (slow infusion required) or IM once/day for 20 days. Adverse effects include nausea, vomiting, malaise; elevated amylase, liver enzymes, or both; and cardiotoxicity (arrhythmias, myocardial depression, heart failure, ECG changes, cardiac arrest). The incidence of side effects increases with age. The drug is

stopped if patients develop cardiotoxicity.

Alternatively, miltefosine may be effective at a dose of 2.5 mg/kg (maximum, 150 mg/day) po once/day for 28 days. Adverse effects include nausea, vomiting, transient aminotransferase elevations, and dizziness. Fluconazole or itraconazole is effective in some cases. Topical paromomycin 2 times a day for 10 to 20 days has been used for *L. major* infections.

Diffuse cutaneous leishmaniasis is relatively resistant to treatment.

Visceral leishmaniasis: Liposomal amphotericin B is the drug of choice in the US and wherever the drug is available; other lipid-associated amphotericin preparations have been used successfully. Immunocompetent patients are given liposomal amphotericin B 3 mg/kg IV once/day for 5 days and then once/day on days 14 and 21. Higher doses and longer regimens are used in patients with AIDS.

Pentavalent antimony compounds are used to treat visceral leishmaniasis in Latin America. Dosing is as for cutaneous disease (see p.), except the drug is given for 28 days.

Drug resistance is an increasing problem with antimonials, particularly in India in patients with visceral leishmaniasis. In such cases, miltefosine 2.5 mg/kg po once/day (maximum 150 mg/day) for 28 days has been effective, but miltefosine resistance has also been reported. Alternatively, amphotericin B deoxycholate 1 mg/kg IV once/day for 15 to 20 days or every other day for up to 8 wk or paromomycin 15 mg/kg IM once/day for 21 days may be used for antimony-sensitive or -resistant strains.

Mucosal leishmaniasis: Pentavalent antimonials (as for visceral leishmaniasis), amphotericin B 0.5 to 1.0 mg/kg once/day or every other day for 8 wk, or miltefosine (as described for visceral leishmaniasis) may be used.

Prevention

For prevention, treatment of cases in a geographic area where humans are a reservoir, reduction of the vector population by spraying residual insecticide (one that has prolonged duration of action) in sites of domestic transmission, and elimination of nonhuman reservoirs may help. People in endemic areas should use insect repellents containing DEET (diethyltoluamide). Insect screens, bed nets, and clothing are more effective if treated with permethrin or pyrethrum because the small sand flies can penetrate mechanical barriers. Vaccines are not currently available.

Malaria

Malaria is infection with *Plasmodium* sp. Symptoms are fever (which may be periodic), chills, sweating, hemolytic anemia, and splenomegaly. Diagnosis is by seeing *Plasmodium* in a peripheral blood smear. Treatment and prophylaxis depend on the species and drug sensitivity and include chloroquine, quinine, the fixed combination of atovaquone and proguanil, mefloquine, doxycycline, and artemisinin derivatives. Patients infected with *P. vivax* and *P. ovale* also receive primaquine to prevent relapse.

Malaria is endemic in Africa, much of South and Southeast Asia, North and South Korea, Mexico, Central America, Haiti, the Dominican Republic, northern South America (including northern parts of Argentina), the Middle East (including Turkey, Syria, Iran, and Iraq), and Central Asia. There are 300 to 500 million infected people worldwide, with 1 to 2 million deaths yearly, most in children < 5 yr in Africa. Malaria once was endemic in the US but has been virtually eliminated. About 1500 cases/yr occur in the US. Nearly all are acquired abroad, but a small number result from blood transfusions or rare autochthonous transmission by local mosquitoes that feed on infected immigrants.

Pathophysiology

The *Plasmodium* species that are spread among humans are

• *P. falciparum*

• *P. vivax*

• *P. ovale*

• *P. malariae*

Also, simian malaria has been reported in humans; *P. knowlesi* is implicated most often. Whether *P. knowlesi* is transmitted from human to human via the mosquito, without the natural intermediate monkey host, has not been determined.

The basic elements of the life cycle are the same for all *Plasmodium* sp. Transmission begins when a female *Anopheles* mosquito feeds on a person with malaria and ingests blood containing gametocytes. During the following 1 to 2 wk, gametocytes inside the mosquito reproduce sexually and produce infective sporozoites. When the mosquito feeds on another human, sporozoites are inoculated and quickly reach the liver and infect hepatocytes. The parasites mature into tissue schizonts within hepatocytes. Each schizont produces 10,000 to 30,000 merozoites, which are released into the bloodstream 1 to 3 wk later when the hepatocyte ruptures. Each merozoite can invade an RBC and there transform into a trophozoite. Trophozoites grow and develop into erythrocyte schizonts; schizonts produce further merozoites, which 48 to 72 h later rupture the RBC and are released in plasma. These merozoites then rapidly invade new RBCs, repeating the cycle. Some trophozoites develop into gametocytes, which are ingested by an *Anopheles* mosquito. They undergo sexual union in the gut of the mosquito, develop into oocysts, and release infective sporozoites, which migrate to the salivary glands.

With *P. vivax* and *P. ovale* (but not *P. falciparum* or *P. malariae*), tissue schizonts may persist as hypnozoites in the liver for up to 3 yr. These dormant forms serve as time-release capsules, which cause relapses and complicate chemotherapy because they are not killed by most antimalarial drugs, which typically act on bloodstream parasites.

The pre-erythrocytic (hepatic) stage of the malarial life cycle is bypassed when infection is transmitted by blood transfusions, by sharing of contaminated needles, or congenitally. Therefore, these modes of transmission do not cause latent disease or delayed recurrences.

Rupture of RBCs during release of merozoites is responsible for the clinical symptoms. If severe, hemolysis causes anemia and jaundice, which are worsened by phagocytosis of infected RBCs in the spleen. Anemia may be severe in *P. falciparum* or chronic *P. vivax* infection but tends to be mild in *P. malariae* infection.

Falciparum malaria: Unlike other forms of malaria, *P. falciparum* causes microvascular obstruction because infected RBCs adhere to vascular endothelial cells. Ischemia develops with resultant tissue hypoxia, particularly in the brain, kidneys, lungs, and GI tract. Hypoglycemia and lactic acidosis are other potential complications.

Resistance to infection: Most West Africans have complete resistance to *P. vivax* because their RBCs lack the Duffy blood group, which is required for the attachment of *P. vivax* to RBCs; many African Americans also have such resistance. The development of *Plasmodium* in RBCs is retarded in patients with hemoglobin S, hemoglobin C, thalassemia, G6PD deficiency, or elliptocytosis.

Previous infections provide partial immunity. Once residents of hyperendemic areas leave, acquired immunity wanes over time (months to years), and symptomatic malaria may develop if they return home and become reinfected.

Symptoms and Signs

The incubation period is usually 12 to 17 days for *P. vivax*, 9 to 14 days for *P. falciparum*, 16 to 18 days or longer for *P. ovale*, and about 1 mo (18 to 40 days) or longer (years) for *P. malariae*. However, some strains of *P. vivax* in temperate climates may not cause clinical illness for months to > 1 yr after infection.

Manifestations common to all forms of malaria include

• Fever and rigor—the malarial paroxysm

• Anemia

• Jaundice

• Splenomegaly

• Hepatomegaly

The malarial paroxysm coincides with release of merozoites from ruptured RBCs. The classic paroxysm starts with malaise, abrupt chills and fever rising to 39 to 41° C, rapid and thready pulse, polyuria, headache, myalgia, and nausea. After 2 to 6 h, fever falls, and profuse sweating occurs for 2 to 3 h, followed by extreme fatigue. Fever is often hectic at the start of infection. In established infections, malarial paroxysms typically occur about every 2 to 3 days depending on the species; intervals are not rigid.

Splenomegaly usually becomes palpable by the end of the first week of clinical disease but may not occur with *P. falciparum*. The enlarged spleen is soft and prone to traumatic rupture. Splenomegaly may decrease with recurrent attacks of malaria as functional immunity develops. After many bouts, the spleen may become fibrotic and firm or, in some patients, becomes massively enlarged (tropical splenomegaly). Hepatomegaly usually accompanies splenomegaly.

P. falciparum causes the most severe disease because of its microvascular effects. It is the only species likely to cause fatal disease if untreated; nonimmune patients may die within days of their initial symptoms. Patients with cerebral malaria may develop symptoms ranging from irritability to seizures and coma. Acute respiratory distress syndrome (ARDS), diarrhea, icterus, epigastric tenderness, retinal hemorrhages, algid malaria (a shocklike syndrome), and severe thrombocytopenia may also occur. Renal insufficiency may result from volume depletion, vascular obstruction by parasitized erythrocytes, or immune complex deposition. Hemoglobinemia and hemoglobinuria resulting from intravascular hemolysis may progress to blackwater fever (so named based on the dark color of the urine), either spontaneously or after treatment with quinine. Hypoglycemia is common and may be aggravated by quinine treatment and associated hyperinsulinemia. Placental involvement may lead to spontaneous abortion, stillbirth, or sometimes congenital infection.

P. vivax, P. ovale, and *P. malariae* typically do not compromise vital organs. Mortality is rare and is mostly due to splenic rupture or uncontrolled hyperparasitemia in asplenic patients. The clinical course with *P. ovale* is similar to that of *P. vivax*. In established infections, temperature spikes occur at 48-h intervals. *P. malariae* infections may cause no acute symptoms, but low-level parasitemia may persist for decades and lead to immune complex-mediated nephritis or nephrosis or tropical splenomegaly; when symptomatic, fever tends to occur at 72-h intervals.

In patients who have been taking chemoprophylaxis (see p.), malaria may be atypical. The incubation period may extend weeks after the drug is stopped. Those infected may develop headache, backache, and irregular fever. Parasites may initially be difficult to find in blood samples.

Diagnosis

• Light microscopy of blood (thin and thick smears)

• Sometimes rapid blood assays that detect *Plasmodium* antigens or enzymes

Fever and chills (particularly recurrent attacks) in a traveler returning from an endemic region should prompt immediate assessment for malaria. Most cases occur within the first 6 mo, but onset may take up to 2 yr or, rarely, longer.

Malaria is typically diagnosed by finding parasites on microscopic examination of thick or thin blood smears. The infecting species (which determines therapy and prognosis) is identified by characteristic features on smears (see
Table 148-1). Blood smears should be repeated at 4- to 6-h intervals if the initial smear is negative.

Thin blood smears stained with Wright-Giemsa stain allow assessment of parasite morphology within RBCs and determination of percentage parasitemia. Thick smears are more sensitive but more difficult to prepare and interpret as the RBCs are lysed before staining.

Commercial rapid assays have been developed to diagnose malaria based on the presence of certain plasmodium antigens or enzymatic activities. Assays may involve detection of a histidine-rich protein 2 (HRP-2) associated with malaria parasites (especially *P. falciparum* and *P. vivax*) and detection of plasmodium-associated lactate dehydrogenase (pLDH). However, the rapid tests are no more sensitive for detecting low levels of parasitemia than evaluation of a blood smear by an experienced microscopist and do not detect dual infections.

PCR and species-specific DNA probes may be used but are not widely available. Serologic tests may reflect prior exposure and are not useful in the diagnosis of acute malaria.

[**Table 148-1.** Diagnostic Features of *Plasmodium* Species in Blood Smears]

Treatment

• Antimalarial drugs chosen by known resistance patterns of strain in area of acquisition

Malaria is particularly dangerous in children < 5 yr (mortality is highest in those < 2 yr), pregnant women, and previously unexposed visitors to endemic areas. In case of a febrile illness during travel in an endemic region, prompt professional medical evaluation is essential; when this is not possible, self-medication with atovaquone-proguanil can be used pending evaluation.

If *P. falciparum* is suspected, therapy should be initiated immediately, even if the initial smear is negative. *P. falciparum* and, more recently, *P. vivax* have become increasingly resistant to antimalarial drugs. Recommended dosages of antimalarial drugs are listed in
Tables 148-2 and
148-3. Common adverse effects and contraindications are listed in
Table 148-4.

[**Table 148-2.** Treatment of Malaria]

Treatment of the acute attack: Chloroquine is the drug of choice against *P. malariae, P. ovale*, and chloroquine-sensitive *P. falciparum* and *P. vivax*. Chloroquine resistance is common among *P. falciparum* strains throughout endemic areas, with the exception of Central America north and west of the Panama Canal, Mexico, Haiti, the Dominican Republic, Paraguay, northern Argentina, North and South Korea, Georgia, Armenia, most of rural China, and some Middle Eastern countries; current location of resistant strains is available from the CDC at http://cdc-malaria.ncsa.uiuc.edu/. Chloroquine resistance is not always complete, but chloroquine should be used only for malaria acquired in areas where *Plasmodium* sp are known to be sensitive.

Artemisinin derivatives, particularly artemether, artesunate, and the new synthetic arteether, are used globally for treatment of acute malaria in regions where chloroquine-resistance is present. They are usually used in combination with a 2nd drug (eg, lumefantrine); in areas where artemisinins were used as monotherapy for many years (China, Viet Nam, along the Thai-Cambodian border), resistance to artemisinins has been confirmed in *P. falciparum*. Artemisinin derivatives act more rapidly than other drugs and are well tolerated.

[**Table 148-3.** Prevention of Malaria]

Although artemisinins are embryotoxic and associated with a low incidence of teratogenicity in animals, they have not been reported to cause birth defects in humans. They are a pregnancy category C drug.

Uncomplicated chloroquine-resistant malaria can also be treated with atovaquoneproguanil. Quinine plus doxycycline has long been used for uncomplicated and complicated chloroquine-resistant infections, but quinine is associated with frequent side effects. If the patient is pregnant, quinine plus clindamycin can be used. Mefloquine is another option, but adverse effects are common.

IV quinidine, quinine dihydrochloride, or artesunate (available from the CDC) is used in patients unable to take oral drugs. If quinidine or quinine is used, hemodynamic and

[**Table 148-4.** Adverse Reactions and Contraindications of Antimalarial Drugs]

ECG monitoring is required; the infusion is slowed or temporarily suspended if the QT interval is > 0.6 sec or the QRS widens > 25% beyond baseline. Parenteral therapy should be continued until oral drug is tolerated. It is customary to supplement quinine and quinidine with doxycycline or clindamycin to prevent late recrudescences. These antibiotics act too slowly to be used alone for the treatment of acute malaria. Halofantrine (not available in the US) may prolong the QT interval and has been associated with sudden death.

Patients with falciparum malaria must be monitored closely for hypoglycemia and proper hydration. Exchange transfusions have been used in some patients with high parasitemia to remove infected RBCs, but there is no uniform agreement on this approach. After successful treatment, patients usually improve in 24 to 48 h, but symptoms can persist for 5 days with *P. falciparum*.

Chloroquine-resistant *P. vivax* is common in Papua New Guinea and Indonesia. It is treated with quinine plus doxycycline or with mefloquine.

Curative therapy for hypnozoites: The hypnozoite stage must be eliminated from the liver with primaquine to prevent relapses of *P. vivax* or *P. ovale* malaria. Primaquine may be given simultaneously with chloroquine or afterward. Some *P. vivax* strains are less sensitive and require repeated treatment with higher doses. Primaquine therapy is not necessary for *P. falciparum* or *P. malariae* because these *Plasmodium* sp do not have a persistent hepatic phase.

Prevention

Prophylactic antimalarial drugs and insect repellants reduce but do not eliminate risk of malaria. Vaccines are under development, but none is currently available.

Prophylaxis against mosquitoes includes using permethrin- or pyrethrum-containing residual insecticide sprays (which have prolonged duration of action) on clothing or in homes and outbuildings, placing screens on doors and windows, using mosquito netting (preferably impregnated with permethrin or pyrethrum) around beds, using mosquito repellents such as DEET (diethyltoluamide), and wearing protective clothing, especially between dusk and dawn, when *Anopheles* mosquitoes are active.

Chemoprophylaxis: Regimens and dosing vary by geographic location and patient characteristics (see Table 148-3). Information for travelers is available from the CDC at www.cdc.gov/malaria/travel/index.htm.

If exposure to *P. vivax* or *P. ovale* is intense or prolonged or if the traveler was splenectomized, a 14-day prophylactic course of primaquine phosphate on return helps reduce the risk of recurrence. The main adverse effect is hemolysis in people with G6PD deficiency. G6PD levels should be determined before the drug is used.

Malaria during pregnancy poses a serious threat to both mother and fetus. Chloroquine can be used in areas where *Plasmodium* sp are susceptible. In general, pregnant women should avoid travel to chloroquine-resistant areas. The safety of mefloquine during pregnancy has not been documented, but limited experience suggests that it may be used when the benefits are judged to outweigh the risks. Doxycycline, atovaquone-proguanil, and primaquine should not be used during pregnancy. Artemisinins

have a short half-life and are not useful for prophylaxis.

Toxoplasmosis

Toxoplasmosis is infection with *Toxoplasma gondii*. Symptoms range from none to benign lymphadenopathy (a mononucleosis-like illness) to life-threatening CNS disease or involvement of other organs in immunocompromised people. Retinochoroiditis, seizures, and intellectual disability occur in congenital infection. Diagnosis is by serologic tests, histology, or PCR. Treatment is most often with pyrimethamine plus either sulfadiazine or clindamycin. Corticosteroids are given concurrently for retinochoroiditis.

Human exposure to toxoplasmosis is common wherever cats are found; 20 to 40% of healthy adults in the US are seropositive. The risk of developing disease is very low except for a fetus infected in utero and people who are or become immunocompromised.

Pathophysiology

T. gondii is ubiquitous in birds and mammals. This obligate intracellular parasite invades and multiplies asexually as tachyzoites within the cytoplasm of any nucleated cell (see Fig. 148-1). When host immunity develops, multiplication of tachyzoites ceases and tissue cysts form; cysts persist in a dormant state for years, especially in brain and muscle. The dormant *Toxoplasma* forms within the cysts are called bradyzoites. Sexual reproduction of *T. gondii* occurs only in the intestinal tract of cats; the resultant oocysts passed in the feces remain infectious in moist soil for months.

Infection can occur by

• Ingestion of oocysts

• Ingestion of tissue cysts

• Transplacental transmission

• Blood transfusion or organ transplantation

Ingestion of oocysts in food or water contaminated with cat feces is the most common mode of oral infection. Infection can also occur by eating raw or undercooked meat containing tissue cysts, most commonly lamb, pork, or rarely beef. After ingestion of oocysts or tissue cysts, tachyzoites are released and spread throughout the body. This acute infection is followed by the development of protective immune responses and the formation of tissue cysts in many organs. The cysts can reactivate, primarily in immunocompromised patients. Toxoplasmosis reactivates in 30 to 40% of AIDS patients who are not taking antibiotic prophylaxis, but the widespread use of trimethoprim/sulfamethoxazole for *Pneumocystis* prophylaxis has dramatically reduced the incidence.

Toxoplasmosis can be transmitted transplacentally if the mother becomes infected during pregnancy or if immunosuppression reactivates a prior infection. Transmission of *Toxoplasma* to a fetus is extraordinarily rare in immunocompetent mothers who have had toxoplasmosis earlier in life. Transmission may occur via transfusion of whole blood or WBCs or via transplantation of an organ from a seropositive donor. In otherwise healthy people, congenital or acquired infection can reactivate in the retina. Past infection confers resistance to reinfection.

Symptoms and Signs

Infections may manifest in several ways:

• Acute toxoplasmosis

• CNS toxoplasmosis

• Congenital toxoplasmosis

• Ocular toxoplasmosis

• Disseminated or non-CNS disease in immunocompromised patients

Acute toxoplasmosis: Acute infection is usually asymptomatic, but 10 to 20% of patients develop bilateral, nontender cervical or axillary lymphadenopathy. A few of these also have a mild flu-like syndrome of fever, malaise, myalgia, hepatosplenomegaly, and less commonly, pharyngitis, which may mimic infectious mononucleosis. Atypical lymphocytosis, mild anemia, leukopenia, and slightly elevated liver enzymes are common. The syndrome may persist for weeks but is almost always self-limited.

CNS toxoplasmosis: Most patients with AIDS or other immunocompromised patients who develop toxoplasmosis due to reactivation present with ring-enhancing intracranial mass lesions or encephalitis. These patients typically have headache, altered mental status, seizures, coma, fever, and sometimes focal neurologic deficits, such as motor or sensory loss, cranial nerve palsies, visual abnormalities, and focal seizures.

Congenital toxoplasmosis: This type results from a primary, often asymptomatic infection acquired by the mother during pregnancy. Women infected before conception ordinarily do not transmit toxoplasmosis to the fetus unless the infection is reactivated during pregnancy

[**Fig. 148-1.** *Toxoplasma gondii* life cycle.]

by immunosuppression. Spontaneous abortion and stillbirth may occur. The percentage of surviving fetuses born with toxoplasmosis depends on when maternal infection is acquired; it increases from 15% during the 1st trimester to 30% during the 2nd to 60% during the 3rd.

Disease in neonates may be severe, particularly if acquired early in pregnancy; symptoms include jaundice, rash, hepatosplenomegaly, and the characteristic tetrad of abnormalities: bilateral retinochoroiditis, cerebral calcifications, hydrocephalus or microcephaly, and psychomotor retardation. Prognosis is poor.

Many children with less severe infections and most infants born to mothers infected during the 3rd trimester appear healthy at birth but are at high risk of seizures, intellectual disability, retinochoroiditis, or other symptoms developing months or even years later.

Ocular toxoplasmosis: This type usually results from congenital infection that is reactivated, often during the teens and 20s, but rarely, it occurs with acquired infections. Focal necrotizing retinitis and a secondary granulomatous inflammation of the choroid occur and may cause ocular pain, blurred vision, and sometimes blindness. Relapses are common.

Disseminated infection and non-CNS involvement: Disease outside the eye and CNS is much less common and occurs primarily in severely immunocompromised patients. They may present with pneumonitis, myocarditis, polymyositis, diffuse maculopapular rash, high fevers, chills, and prostration. In toxoplasmic pneumonitis, diffuse interstitial infiltrates may progress rapidly to consolidation and cause respiratory failure, whereas endarteritis may lead to infarction of small lung segments. Myocarditis, in which conduction defects are common but often asymptomatic, may rapidly lead to heart failure. Untreated disseminated infections are usually fatal.

Diagnosis

• Serologic testing

• For CNS involvement, CT or MRI and lumbar puncture

The diagnosis is usually made serologically using an indirect fluorescent antibody (IFA) test or enzyme immunoassay (EIA) for IgG and IgM antibodies. Specific IgM antibodies appear during the first 2 wk of

acute illness, peak within 4 to 8 wk, and eventually become undetectable, but they may be present for as long as 18 mo after acute infection. IgG antibodies arise more slowly, peak in 1 to 2 mo, and may remain high and stable for months to years. Specific IgM antibodies with low IgG are consistent with recent infection in immunocompetent patients. Acute infection should also be suspected if the IgG is positive in immunocompromised patients with encephalitis. *Toxoplasma*-specific IgG antibody levels in AIDS patients with *Toxoplasma* encephalitis are usually low to moderate but may be absent; IgM antibodies are not present. Past infection in a healthy person typically produces a negative IgM test and a positive IgG test. In patients with retinochoroiditis, low titers of IgG antibodies are usually present, but IgM antibodies are not detected.

The diagnosis of acute toxoplasmosis during pregnancy and in the fetus or neonate can be difficult, and consultation with an expert is recommended. If the patient is pregnant and IgG and IgM are positive, an IgG avidity test should be done. High avidity antibodies in the first 12 to 16 wk of pregnancy essentially rules out an infection acquired during gestation. But a low IgG avidity result cannot be interpreted as indicating recent infection because some patients have persistent low IgG avidity for many months after infection. Suspected recent infection in a pregnant woman should be confirmed before intervention by having samples tested at a toxoplasmosis reference laboratory. If the patient has clinical illness compatible with toxoplasmosis but the IgG titer is low, a follow-up titer 2 to 3 wk later should show an increase in antibody titer if the illness is due to acute toxoplasmosis, unless the host is severely immunocompromised.

In general, detection of specific IgM antibody in neonates suggests congenital infection. Maternal IgG crosses the placenta, but IgM does not. Detection of *Toxoplasma*-specific IgA antibodies is more sensitive than IgM in congenitally infected infants, but it is available only at special reference facilities (eg, Palo Alto Medical Foundation [telephone 650-853-4828]). They should be consulted when fetal or congenital infection is suspected.

Toxoplasma are occasionally demonstrated histologically. Tachyzoites, which are present during acute infection, take up Giemsa or Wright's stain but may be difficult to find in routine tissue sections. Tissue cysts do not distinguish acute from chronic infection. *Toxoplasma* must be distinguished from other intracellular organisms, such as *Histoplasma*, *Trypanosoma cruzi*, and *Leishmania*. PCR tests for parasite DNA in blood, CSF, or amniotic fluid are available at several reference laboratories. PCR-based analysis of amniotic fluid is the preferred method to diagnose toxoplasmosis during pregnancy.

If CNS toxoplasmosis is suspected, patients should have head CT with contrast agent, MRI, or both plus a lumbar puncture if there are no signs of increased intracranial pressure. MRI is more sensitive than CT. CSF may show lymphocytic pleocytosis and elevated protein levels. CT typically shows single or multiple dense, rounded, ring-enhancing lesions. Although these lesions are not pathognomonic, their presence in patients with AIDS and CNS symptoms warrants a trial of chemotherapy for *T. gondii*. If the suspected diagnosis of toxoplasmosis is correct, clinical or radiographic improvement should become evident within 7 to 14 days. If symptoms persist, a brain biopsy should be considered.

Treatment

• Pyrimethamine plus sulfadiazine (when treatment is indicated)

Most immunocompetent patients do not require therapy unless visceral disease is present or severe symptoms persist. However, specific treatment is indicated for acute toxoplasmosis of neonates, pregnant women, and immunocompromised patients.

The most effective regimen in immunocompetent patients is pyrimethamine plus sulfadiazine. Dosage for pyrimethamine is 50 to 100 mg po q 12 h for 1 day, then 25 to 100 mg once/day for 3 to 4 wk in adults (1 mg/kg q 12 h for 3 days, then 1 mg/kg once/day for 4 wk in children; maximum 25 mg/day). Dosage for sulfadiazine is 1 to 1.5 g po qid for 3 to 4 wk in adults (25 to 50 mg/kg qid for 4 wk in children). Higher doses of pyrimethamine are used in HIV-infected patients with CNS toxoplasmosis. Some clinicians use a loading dose of pyrimethamine 200 mg the first day, then 50 to 100 mg/day plus sulfadiazine for 4 to 6 wk. In patients who have or develop sulfonamide hypersensitivity, clindamycin 600 to 800 mg po tid is given instead of sulfonamides. Another option is atovaquone 1500 mg q 12 h plus pyrimethamine, starting with

a 200-mg loading dose followed by 75 mg/day for 6 wk. Relapses of toxoplasmosis are common in patients with AIDS, and suppressive treatment should continue indefinitely unless the CD4 count increases and remains above 200/μL. Pyrimethamine bone marrow suppression can be minimized with leucovorin (also called folinic acid; not folate, which blocks the therapeutic effect). The dosage is 10 to 25 mg po once/day. Patients with ocular toxoplasmosis should also be given corticosteroids.

Treatment of pregnant women with primary infection can decrease the incidence of fetal infection. Spiramycin 1 g po tid or qid has been used safely to reduce transmission in pregnant women during the 1st trimester (available from the FDA [telephone 301-827-2335]), but spiramycin is less active than pyrimethamine plus sulfonamide and does not cross the placenta. Spiramycin is continued until fetal infection is documented or excluded at the end of the 1st trimester. If no transmission has occurred, spiramycin can be continued to term. If the fetus is infected, pyrimethamine plus sulfadiazine is used. Pyrimethamine is a potent teratogen and should not be used during the 1st trimester. Consultation with an infectious diseases expert is recommended.

Congenitally infected infants should be treated with pyrimethamine every 2 to 3 days and with sulfadiazine once/day for about a year. Infants should also receive leucovorin while receiving pyrimethamine and for 1 wk after pyrimethamine is stopped to prevent bone marrow suppression.

Prevention

Washing hands thoroughly after handling raw meat, soil, or cat litter is essential. Food possibly contaminated with cat feces should be avoided. Meat should be cooked to 165 to 170° F.

Chemoprophylaxis is recommended for patients with HIV and a positive IgG *T. gondii* serologic test once CD4+ cell counts are < 100/μL. One double-strength tablet of trimethoprim/sulfamethoxazole once/day, which also is prophylactic against *Pneumocystis jirovecii*, is one regimen. Alternatively, pyrimethamine plus dapsone or atovaquone with or without pyrimethamine can be used.

Chapter 149. Viruses

Introduction

Viruses are the smallest parasites, ranging from 0.02 to 0.3 μm. They depend completely on cells (bacterial, plant, or animal) to reproduce. Viruses have an outer cover of protein, and sometimes lipid, and an RNA or DNA core. For infection to occur, the virus first attaches to the host cell. The viral DNA or RNA then enters the host cell and separates from the outer cover (uncoating) and replicates inside the host cell in a process that requires specific enzymes. Most RNA viruses replicate their nucleic acid in the cytoplasm, whereas most DNA viruses replicate in the nucleus. The host cell typically dies, releasing new viruses that infect other host cells.

The consequences of viral infection vary considerably. Many infections cause acute illness after a brief incubation period, but some are asymptomatic or cause minor symptoms that may not be recognized except in retrospect. Many viral infections are cleared by the body's defenses, but some remain in a latent state. In latent infection, viral RNA or DNA remains in host cells but does not cause disease for a long time, sometimes for many years. Latent viral infections may be transmissible during the asymptomatic period, facilitating person-to-person spread. Sometimes a trigger (particularly immunosuppression) causes reactivation. Common viruses that remain latent include

• Herpesviruses

• HIV

• Papovaviruses

Some disorders are caused by viral reactivation in the CNS after a very long latency period. These diseases include progressive multifocal leukoencephalopathy (due to the JC virus, a polyomavirus), subacute sclerosing panencephalitis (due to the measles virus), and progressive rubella panencephalitis (due to rubella virus). Creutzfeldt-Jakob disease and bovine spongiform encephalopathy were formerly termed slow viral diseases because they have lengthy incubations (years), but they are now known to be caused by prions; prions are proteinaceous disease-causing agents that are not bacterial, fungal, or viral and that contain no genetic material (see p.).

Several hundred different viruses infect humans. Viruses that infect primarily humans often spread via respiratory and enteric excretions. Some are transmitted sexually and through transfer of blood. Some viruses are transmitted via arthropod vectors. Viruses exist worldwide, but their spread is limited by inborn resistance, prior immunizing infections or vaccines, sanitary and other public health control measures, and prophylactic antiviral drugs.

Zoonotic viruses (see) pursue their biologic cycles chiefly in animals; humans are secondary or accidental hosts. These viruses are limited to areas and environments able to support their nonhuman natural cycles of infection (vertebrates, arthropods, or both).

Viruses and cancer: Some viruses are oncogenic and predispose to certain cancers:

• **Papillomavirus:** Cervical and anal carcinomas

• **Human T-lymphotropic virus 1:** Certain types of human leukemia and lymphoma

• **Epstein-Barr virus:** Nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin lymphoma, and lymphomas in immunosuppressed organ transplant recipients

• **Hepatitis B and C viruses:** Hepatocellular carcinoma

• **Human herpesvirus 8:** Kaposi's sarcoma, primary effusion lymphomas, and multicentric Castleman disease (a lymphoproliferative disorder)

Diagnosis

Some viral disorders can be diagnosed clinically (eg, by well-known viral syndromes such as measles, rubella, roseola infantum, erythema infectiosum, and chickenpox) or epidemiologically (eg, during epidemic outbreaks such as influenza). Definitive laboratory diagnosis is necessary mainly when specific treatment may be helpful or when the agent may be a public health threat (eg, HIV). Typical hospital laboratories can test for some viruses, but for less common disorders (eg, rabies, Eastern equine encephalitis), specimens must be sent to state health laboratories or the Centers for Disease Control and Prevention.

Serologic examination during acute and convalescent stages is sensitive and specific but slow; more rapid diagnosis can sometimes be made using culture, PCR, or viral antigen tests. Histopathology with electron (not light) microscopy can sometimes help. For specific diagnostic procedures, see Ch. 130.

Treatment

Antiviral drugs: Progress in the use of antiviral drugs is occurring rapidly. Antiviral chemotherapy can be directed at various phases of viral replication: It can interfere with viral particle attachment to host cell membranes or uncoating of viral nucleic acids, inhibit a cellular receptor or factor required for viral replication, or block specific virus-coded enzymes and proteins that are produced in the host cells and that are essential for viral replication but not for normal host cell metabolism.

Antiviral drugs are most often used therapeutically or prophylactically against herpesviruses (including cytomegalovirus—see Ch. 151), respiratory viruses (see Ch. 150), and HIV (see Ch. 154). However, some drugs are effective against many different kinds of viruses. Some drugs active against HIV are used for other viral infections such as hepatitis B.

Interferons: Interferons are compounds released from infected host cells in response to viral or other foreign antigens. There are many different interferons, which have numerous effects such as blocking translation and transcription of viral RNA and stopping viral replication without disturbing normal host cell function. Interferons are sometimes given attached to polyethylene glycol (pegylated formulations), allowing slow, sustained release of the interferon.

Viral disorders sometimes treated with interferon therapy include

• Chronic hepatitis B and C

• Condyloma acuminata

• Hairy cell leukemia

• Kaposi's sarcoma

Adverse effects of interferons include fever, chills, weakness, and myalgia, typically starting 7 to 12 h after the first injection and lasting up to 12 h. Depression, hepatitis, and, when high doses are used, bone marrow suppression are also possible.

Prevention

Vaccines: Vaccines (see p. 1170) work by stimulating native immunity. Viral vaccines in general use include hepatitis A, hepatitis B, human papillomavirus, influenza, measles, mumps, poliomyelitis, rabies, rotavirus, rubella, varicella, and yellow fever. Adenovirus and smallpox vaccines are available but used only in high-risk groups (eg, military recruits).

Immune globulins: Immune globulins (see p. 1178) are available for passive immune prophylaxis in limited situations. They can be used preexposure (eg, for hepatitis A), postexposure (eg, for rabies or hepatitis), and for treating disease (eg, eczema vaccinatum).

Protective measures: Many viral infections can be prevented by commonsense protective measures (which vary depending on the transmission mode of a given agent). Important measures include hand washing, appropriate food preparation and water treatment, avoidance of contact with sick people, and safe-sex practices. For infections with an insect vector (eg, mosquitoes, ticks), avoiding the vector is important.

Types of Viral Disorders

Categorizing viral infections by the organ system most commonly affected (eg, lungs, GI tract, skin, liver, CNS, mucous membranes) can be clinically useful, although certain viral disorders (eg, mumps) are hard to categorize. Many specific viruses and the disorders they cause are also discussed elsewhere in THE MANUAL.

Respiratory infections: The most common viral infections are probably URIs. Respiratory infections are more likely to cause severe symptoms in infants, the elderly, and patients with a lung or heart disorder.

Respiratory viruses include influenza viruses (A, B, C), parainfluenza viruses 1 through 4, adenoviruses, respiratory syncytial virus, and rhinoviruses (see Table 149-1 and Ch. 150). They are typically spread from person to person by contact with infected respiratory droplets.

GI infections: Gastroenteritis is usually caused by viruses (Ch. 16) and transmitted from person-to person by the oral-fecal route. Age group primarily affected depends on the virus:

• **Rotavirus:** Children

• **Norovirus:** Older children and adults

• **Astrovirus:** Usually infants and young children

• **Adenovirus 40 and 41:** Infants

• **Coronavirus-like agents:** Infants

Local epidemics may occur in children, particularly during colder months.

The main symptoms are vomiting and diarrhea.

No specific treatment is recommended, but supportive care, particularly rehydration, is important.

A rotavirus vaccine that is effective against most pathogenic strains is part of the recommended infant vaccination schedule (see Table 268-10 on p. 2718). Hand washing and good sanitation measures can help prevent spread.

Exanthematous infections: Some viruses cause only skin lesions (as in molluscum contagiosum and warts—see Ch. 84); others also cause systemic manifestations or lesions

[**Table 149-1.** Some Respiratory Viruses]

elsewhere in the body (see Table 149-2). Transmission is typically from person to person; alphaviruses have a mosquito vector.

Hepatic infections: At least 5 specific viruses (hepatitis A, B, C, D, and E viruses) can cause hepatitis; each causes a specific type of hepatitis (see Table 149-3 and Ch. 28). Hepatitis D virus can infect only when hepatitis B is present. Transmission is from person to person by contact with infected blood or body secretions or by the fecal-oral route for hepatitis A and E.

Other viruses can affect the liver as part of their disease process. Common examples are cytomegalovirus, Epstein-Barr virus, and yellow fever virus. Less common examples are echovirus, coxsackievirus, and herpes simplex, rubeola, rubella, and varicella viruses.

[**Table 149-2.** Some Exanthematous Viruses]

[**Table 149-3.** Viral Hepatitis]

Neurologic infections: Most cases of encephalitis are caused by viruses (see Table 149-4 and p. 1726). Many of these viruses are transmitted to humans by blood-eating arthropods, mainly mosquitoes and ticks (see Ch. 153); these viruses are called arboviruses (arthropod-borne viruses). For such infections, prevention includes avoiding mosquito and tick bites.

Hemorrhagic fevers: Certain viruses cause fever and a bleeding tendency (see Table 149-5 and Ch. 153). Transmission may involve mosquitoes, ticks, or contact with infected animals (eg, rodents, monkeys, bats) and people. Prevention involves avoiding the means of transmission.

Cutaneous or mucosal infections: Some viruses cause skin or mucosal lesions that recur and may become chronic (see Table 149-7). Mucocutaneous infections are the most common type of herpes simplex virus infection (see p. 1417). Human papillomavirus causes warts (see pp. 715 and 1470); some subtypes cause cervical cancer (see p. 2576). Transmission is by person-to-person contact.

Multisystem diseases: Enteroviruses, which include coxsackieviruses and echoviruses

[**Table 149-4.** Some Neurologic Viruses]

[**Table 149-5.** Some Viruses that Cause Hemorrhagic Fever]

(see Ch. 152), can cause various multisystem syndromes, as can cytomegaloviruses (see Table 149-7 and p. 1416). Transmission is by the fecal-oral route.

Nonspecific febrile illness: Some viruses cause nonspecific symptoms, including fever, malaise, headaches, and myalgia (see Tables 149-8 and 153-1). Transmission is usually by an insect or arthropod vector.

Rift Valley fever rarely progresses to ocular disorders, meningoencephalitis, or a hemorrhagic form (which has a 50% mortality rate).

[
Table 149-6. Some Viruses that Cause Recurrent or Chronic Skin or Mucosal Lesions]

[**Table 149-7.** Some Viruses that Cause Multisystem Disease]

[**Table 149-8.** Some Viruses that Cause Nonspecific Acute Febrile Illness]

Chapter 150. Respiratory Viruses

Introduction

(See also Bronchiolitis on p. 2878, Croup on p. 2879, and Pneumonia on p. 1923.)

Viral infections commonly affect the upper or lower respiratory tract. Although these infections can be classified by the causative virus (eg, influenza), they are generally classified clinically according to syndrome (eg, the common cold, bronchiolitis, croup). Although specific pathogens commonly cause characteristic clinical manifestations (eg, rhinovirus typically causes the common cold, respiratory syncytial virus [RSV] typically causes bronchiolitis), each can cause many of the viral respiratory syndromes (see Table 150-1).

Severity of viral respiratory illness varies widely; severe disease is more likely in the elderly and infants. Morbidity may result directly from viral infection or may be indirect,

[**Table 150-1.** Causes of Common Viral Respiratory Syndromes]

due to exacerbation of underlying cardiopulmonary conditions or bacterial superinfection of the lung, paranasal sinuses, or middle ear.

Diagnosis

Detection of viral pathogens by PCR, culture, or serologic tests is generally too slow to be useful for patient care but is useful for epidemiologic surveillance. More rapid diagnostic tests are available for influenza and RSV, but the utility of these tests for routine care is not clear; they should be reserved for situations in which pathogen-specific diagnosis affects clinical management. Management decisions are usually based on clinical data and epidemiology.

Treatment

Treatment of viral respiratory infections is usually supportive. Antibacterial drugs are ineffective against viral pathogens, and prophylaxis against secondary bacterial infections is not recommended. Antibiotics should be given only when secondary bacterial infections develop. In patients with chronic lung disease, antibiotics may be given with less restriction.

Aspirin should not be used in patients who are ≤18 yr and have respiratory infections because Reye's syndrome is a risk.

Some patients continue to cough for weeks after resolution of an URI; these symptoms may lessen with use of an inhaled bronchodilator or corticosteroids.

In some cases, antiviral drugs are useful. Amantadine, rimantadine, oseltamivir, and zanamivir are effective for influenza. Ribavirin, a guanosine analog that inhibits replication of many RNA and DNA viruses, may be considered for severely immunocompromised patients with lower respiratory tract infection due to RSV.

Adenovirus Infections

Infection with one of the many adenoviruses may be asymptomatic or result in specific syndromes, including mild respiratory infections, keratoconjunctivitis, gastroenteritis, cystitis, and primary pneumonia. Diagnosis is clinical. Treatment is supportive.

Adenoviruses are DNA viruses classified according to 3 major capsid antigens (hexon, penton, and fiber). Adenoviruses are commonly acquired by contact with secretions (including those on fingers of infected people) from an infected person or by contact with a contaminated object (eg, towel, instrument). Infection may be airborne or waterborne (eg, acquired while swimming). Asymptomatic respiratory or GI viral

shedding may continue for months, or even years.

Symptoms and Signs

In immunocompetent hosts, most adenovirus infections are asymptomatic; when infections are symptomatic, a broad spectrum of clinical manifestations is possible. The most common syndrome, especially in children, involves fever that tends to be > 39° C and to last > 5 days. Sore throat, cough, rhinorrhea, or other respiratory symptoms may occur. A separate syndrome involves conjunctivitis, pharyngitis, and fever (pharyngoconjunctival fever). Rare adenoviral syndromes in infants include severe bronchiolitis (see p. 2878) and pneumonia. In closed populations of young adults (eg, military recruits), outbreaks of respiratory illness may occur; symptoms include fever and lower respiratory tract symptoms, usually tracheobronchitis but occasionally pneumonia.

Epidemic keratoconjunctivitis (see p. 581) is sometimes severe and occurs sporadically and in epidemics. Conjunctivitis is frequently bilateral. Preauricular adenopathy may develop. Chemosis, pain, and punctate corneal lesions that are visible with fluorescein staining may be present. Systemic symptoms and signs are mild or absent. Epidemic keratoconjunctivitis usually resolves within 3 to 4 wk, although corneal lesions may persist much longer.

Nonrespiratory adenoviral syndromes include hemorrhagic cystitis, diarrhea in infants, and meningoencephalitis.

Most patients recover fully. Even severe primary adenoviral pneumonia is not fatal except for rare fulminant cases, predominantly in infants, military recruits, and immunocompromised patients.

Diagnosis

• Clinical evaluation

Laboratory diagnosis of adenovirus infection rarely affects management. During the acute illness, virus can be isolated from respiratory and ocular secretions and frequently from stool and urine. A 4-fold rise in the serum antibody titer indicates recent adenoviral infection.

Treatment

• Symptomatic treatment

Treatment is symptomatic and supportive.

To minimize transmission, heath care practitioners should change gloves and wash hands after examining infected patients, sterilize instruments adequately, and avoid using ophthalmologic instruments in multiple patients.

Prevention

Vaccines containing live adenovirus types 4 and 7, given orally in an enteric-coated capsule, can reduce lower respiratory disease in military populations; however, these vaccines are no longer available.

Common Cold

(Upper Respiratory Infection; Coryza)

The common cold is an acute, usually afebrile, self-limited viral infection causing upper respiratory symptoms, such as rhinorrhea, cough, and sore throat. Diagnosis is clinical. Hand washing helps prevent its spread. Treatment is supportive.

About 50% of all colds are caused by one of the > 100 serotypes of rhinoviruses. Coronaviruses cause some outbreaks, and infections caused by influenza, parainfluenza, enterovirus, adenovirus, respiratory

syncytial viruses, and metapneumoviruses may also manifest as the common cold, particularly in patients who are experiencing reinfection.

Rhinovirus infections are most common during fall and spring and are less common during winter. Rhinoviruses are most efficiently spread by direct person-to-person contact, although spread may also occur via large-particle aerosols.

The most potent deterrent to infection is the presence of specific neutralizing antibodies in the serum and secretions, induced by previous exposure to the same or a closely related virus. Susceptibility to colds is not affected by exposure to cold temperature, host health and nutrition, or upper respiratory tract abnormalities (eg, enlarged tonsils or adenoids).

Symptoms and Signs

After an incubation period of 24 to 72 h, symptoms begin with a "scratchy" or sore throat, followed by sneezing, rhinorrhea, nasal obstruction, and malaise. Temperature is usually normal, particularly when the pathogen is a rhinovirus or coronavirus. Nasal secretions are watery and profuse during the first days but then become more mucoid and purulent. Mucopurulent secretions do not indicate a bacterial superinfection. Cough is usually mild but often lasts into the 2nd wk. Most symptoms due to uncomplicated colds resolve within 10 days. Colds may exacerbate asthma and chronic bronchitis.

Purulent sputum or significant lower respiratory tract symptoms are unusual with rhinovirus infection. Purulent sinusitis and otitis media may result from the viral infection itself or from secondary bacterial infection.

Diagnosis

• Clinical evaluation

Diagnosis is generally made clinically and presumptively, without diagnostic tests. Allergic rhinitis is the most important consideration in differential diagnosis.

Treatment

• Symptomatic treatment

No specific treatment exists. Antipyretics and analgesics may relieve fever and sore throat. Nasal decongestants may reduce nasal obstruction. Topical nasal decongestants are more effective than oral decongestants, but the use of topical drugs for > 3 to 5 days may result in rebound congestion. Rhinorrhea may be relieved with 1st-generation antihistamines (eg, chlorpheniramine) or intranasal ipratropium bromide (2 sprays of a 0.03% solution bid or tid); however, these drugs should be avoided in the elderly and people with benign prostatic hypertrophy or glaucoma. First-generation antihistamines frequently cause sedation, but 2nd-generation (nonsedating) antihistamines are ineffective for treating the common cold. Antihistamines and decongestants are not recommended for children < 4 yr.

Zinc, echinacea, and vitamin C have all been evaluated as common cold therapies, but none has been clearly shown to be beneficial.

Prevention

There are no vaccines. Polyvalent bacterial vaccines, citrus fruits, vitamins, ultraviolet light, glycol aerosols, and other folk remedies do not prevent the common cold. Hand washing and use of surface disinfectant in a contaminated environment may reduce spread of infection.

Antibiotics should not be given unless there is clear evidence of secondary bacterial infection. In patients with chronic lung disease, antibiotics may be given with less restriction.

Influenza

(Flu; Grippe; Grip)

Influenza is a viral respiratory infection causing fever, coryza, cough, headache, and malaise. Mortality is possible during seasonal epidemics, particularly among high-risk patients (eg, those who are institutionalized, at the extremes of age, have cardiopulmonary insufficiency, or are in late pregnancy); during pandemics, even healthy, young patients may die. Diagnosis is usually clinical and depends on local epidemiologic patterns. High-risk patients, their caregivers and household contacts, health care practitioners, all people ≥ 50 yr, and all children aged 6 mo to 18 yr should receive annual influenza vaccination. Antiviral treatment reduces the duration of illness by about 1 day and should be specifically considered for high-risk patients.

Influenza refers to illness caused by the influenza viruses, but the term is commonly and incorrectly used to refer to similar illnesses caused by other viral respiratory pathogens. Influenza viruses are classified as types A, B, or C by their nucleoproteins and matrix proteins. Influenza C virus infection does not cause typical influenza illness and is not discussed here.

Influenza antigens: Hemagglutinin (HA) is a glycoprotein on the influenza surface that allows the virus to bind to cellular sialic acid and fuse with the host membrane. Neuraminidase (NA), another surface glycoprotein, enzymatically removes sialic acid, promoting viral dispersion from the infected cell.

Antigenic drift refers to relatively minor mutations in HA and NA of influenza A and B that result in the frequent emergence of new viral strains. The result is decreased protection by antibody generated to the previous strain.

Antigenic shift refers to a major change in NA or HA that occurs in influenza A (antigenic shift) at infrequent intervals (10 to 40 yr during the last century); as a result, the population has no immunity to the new virus, and pandemic influenza may occur.

Epidemiology

Influenza causes widespread sporadic illness yearly during fall and winter in temperate climates. Epidemics in the US occur about every 2 to 3 yr, most often caused by influenza A viruses. Pandemics due to new influenza A serotypes may cause particularly severe disease. Influenza B viruses typically cause mild disease but can cause epidemics with moderate or severe disease, usually in 3- to 5-yr cycles. Although most influenza epidemics result from a single serotype, different influenza viruses may appear sequentially in one location or may appear simultaneously, with one virus predominating in one location and another virus predominating elsewhere.

Seasonal epidemics often occur in 2 waves—the first in schoolchildren and their household contacts (generally younger people) and the 2nd mostly in housebound or institutionalized people, particularly the elderly.

Influenza viruses may be spread by airborne droplets, person-to-person contact, or contact with contaminated items. Airborne spread appears to be the most important mechanism.

At-risk groups: Certain patients are at high risk of complications from influenza:

• Children < 4 yr

• Adults > 65 yr

• People with chronic medical disorders (eg, cardiopulmonary disease, diabetes mellitus, renal or hepatic insufficiency, hemoglobinopathies, immuodeficiency)

• Women in the 2nd or 3rd trimester of pregnancy

• Patients with disorders that impair handling of respiratory secretions (eg, cognitive dysfunction,

neuromuscular disorders, stroke, seizure disorders)

• Patients ≤ 18 yr taking aspirin (because Reye's syndrome is a risk)

Morbidity and mortality in these patients may be due to exacerbation of underlying illness, acute respiratory distress syndrome, primary influenza pneumonia, or secondary bacterial pneumonia.

Symptoms and Signs

The incubation period ranges from 1 to 4 days with an average of about 48 h. In mild cases, many symptoms are like those of a common cold (eg, sore throat, rhinorrhea); mild conjunctivitis may also occur. Typical influenza in adults is characterized by sudden onset of chills, fever, prostration, cough, and generalized aches and pains (especially in the back and legs). Headache is prominent, often with photophobia and retrobulbar aching. Respiratory symptoms may be mild at first, with scratchy sore throat, substernal burning, nonproductive cough, and sometimes coryza. Later, lower respiratory tract illness becomes dominant; cough can be persistent, raspy, and productive. GI symptoms may occur and appear to be more common with the 2009 pandemic H1N1 strain. Children may have prominent nausea, vomiting, or abdominal pain, and infants may present with a sepsis-like syndrome.

After 2 to 3 days, acute symptoms rapidly subside, although fever may last up to 5 days. Cough, weakness, sweating, and fatigue may persist for several days or occasionally for weeks.

Complications: Pneumonia is suggested by a worsening cough, bloody sputum, dyspnea, and rales. Secondary bacterial pneumonia is suggested by persistence or recurrence of fever and cough after the primary illness appears to be resolving.

Encephalitis, myocarditis, and myoglobinuria, sometimes with renal failure, develop infrequently after influenza A or B infection. Reye's syndrome (see p.),—characterized by encephalopathy; fatty liver; elevation of liver enzymes, ammonia, or both; hypoglycemia; and lipidemia—often occurs during epidemics of influenza B, particularly in children who have ingested aspirin.

Diagnosis

• Clinical evaluation

• Sometimes rapid diagnostic testing

• Pulse oximetry and chest x-ray for patients with severe respiratory symptoms

The diagnosis is generally made clinically in patients with a typical syndrome when influenza is known to be present in the community. Although many rapid diagnostic tests are available, their sensitivities and specificities vary widely in different studies and they usually add little to patient management. Diagnostic tests should be done when results will affect clinical decisions. Reverse transcriptase-PCR (RT-PCR) assays are sensitive and specific and can differentiate influenza types and subtypes. If this assay is quickly available, results may be used to select appropriate antiviral therapy. These tests are also useful to determine whether outbreaks of respiratory disease are due to influenza. Cell culture of nasopharyngeal swabs or aspirates takes several days and is not useful for patient management decisions.

If patients have lower respiratory tract symptoms and signs (eg, dyspnea, rales noted during lung examination), pulse oximetry to detect hypoxemia and a chest x-ray to detect pneumonia should be done. Primary influenza pneumonia appears as focal or diffuse interstitial infiltrates or as acute respiratory distress syndrome. Secondary bacterial pneumonia is more likely to be lobar or segmental.

Prognosis

Most patients recover fully, although full recovery often takes 1 to 2 wk. However, influenza and influenza-related pneumonia are important causes of increased morbidity or mortality in high-risk patients. Use of

antiviral treatment in these patients appears to reduce the incidence of lower respiratory disease and hospitalization. Appropriate antibacterial therapy decreases the mortality rate due to secondary bacterial pneumonia.

Treatment

• Symptomatic treatment

• Sometimes antiviral drugs

Treatment for most patients is symptomatic, including rest, hydration, and antipyretics as needed, but aspirin is avoided in patients ≤ 18 yr. Complicating bacterial infections require appropriate antibiotics.

Drugs for influenza: Antiviral drugs given within 1 to 2 days of symptom onset decrease the duration of fever, severity of symptoms, and time to return to normal activity. Treatment with antiviral drugs is recommended for high-risk patients who develop influenza-like symptoms; this recommendation is based on data suggesting that early treatment may prevent complications in these patients.

Drugs for influenza include the following:

• Oseltamivir and zanamivir (neuraminidase inhibitors)

• Amantadine and rimantadine (adamantanes)

Neuraminidase inhibitors interfere with release of influenza virus from infected cells and thus halt spread of infection.

Adamantanes block the M2 ion channel and thus interfere with viral uncoating inside the cell. They are effective only against influenza A viruses (influenza B viruses lack the M2 protein).

Choice of antiviral drug is complicated by resistance of different influenza types and subtypes to different drugs (see Table 150-2). If RT-PCR testing is rapidly available, results can be used to direct treatment. If RT-PCR is not available, patients may be treated with zanamivir alone or with rimantadine plus oseltamivir.

Zanamivir is given by an inhaler, 2 puffs (10 mg) bid; it can be used in adults and children ≥ 7 yr. Zanamivir sometimes causes bronchospasm and should not be given to patients with reactive airway disease; some people cannot use the inhalation device.

Oseltamivir 75 mg po bid is given to patients > 12 yr; lower doses may be used in children as young as 1 yr. Oseltamivir may cause occasional nausea and vomiting. In children, oseltamivir may decrease the incidence of otitis media; however, no other data clearly show that treatment of influenza prevents complications.

Rimantadine is the preferred adamantane because it has fewer side effects and is better tolerated. Treatment is stopped 1 to 2 days after symptoms resolve or after 3 to 5 days. For rimantadine or amantadine, 100 mg po bid can be used. To avoid adverse effects due to drug accumulation, clinicians reduce the dose for children (2.5 mg/kg bid to a maximum of 150 mg/day for children < 10 yr or 200 mg/day for children ≥ 10 yr). In patients with impaired renal function, dose is adjusted according to creatinine clearance. The dose of rimantadine should not exceed 100 mg/day if patients have hepatic dysfunction. Dose-related nervousness, insomnia, or other CNS effects occur in about 10% of people receiving amantadine and in about 2% of people receiving rimantadine. These effects usually occur within 48 h after starting the drug, are more prominent in the elderly and in patients with CNS diseases or impaired renal function, and often resolve during continued use. Anorexia, nausea, and constipation may also occur.

Prevention

Influenza infections can largely be prevented by

• Annual vaccination

• Sometimes chemoprophylaxis (ie, with antiviral drugs)

[**Table 150-2.** Drug Sensitivities of Various Influenza Strains]

Prevention is indicated for all patients, but is especially important for high-risk patients and health care practitioners.

Vaccines: Vaccines are modified annually to include the most prevalent strains (usually 2 strains of influenza A and 1 of influenza B). When the vaccine contains the same HA and NA as the strains in the community, vaccination decreases infections by 70 to 90% in healthy adults. In the institutionalized elderly, vaccines are less effective for prevention but decrease the rate of pneumonia and death by 60 to 80%. Vaccine-induced immunity is decreased by antigenic drift and is absent if there is antigenic shift.

There are 2 types of vaccine:

• Trivalent inactivated influenza vaccine (TIV)

• Live-attenuated influenza vaccine (LAIV)

TIV is given by IM injection. Patients aged 6 mo to 35 mo are given 0.25 mL, and those ≥ 3 yr are given 0.5 mL. Adverse effects are usually limited to mild pain at the injection site; it lasts no more than a few days. Fever, myalgia, and other systemic effects are uncommon.

LAIV is given intranasally at a dose of 0.25 mL in each nostril. It may be used for healthy people aged 2 to 49 yr. The vaccine is not recommended for high-risk patients, pregnant women, household contacts of patients with severe immunodeficiency (eg, with hematopoietic stem cell transplants), or children who are receiving long-term aspirin therapy. Adverse effects associated with the vaccine are mild; rhinorrhea is the most common, and mild wheezing may occur. LAIV should not be given to children who are < 5 yr and have reactive airway disease (eg, known asthma, recurrent or recent wheezing episodes).

For both vaccines, children who are < 8 yr and have not been vaccinated should be given a primary dose and a booster dose 1 mo apart.

Vaccination recommendations: Annual vaccination is recommended for

• All children aged 6 mo to 18 yr

• All people ≥ 50 yr

• People who are aged 19 to 49 yr and have chronic health disorders (eg, immunosuppression, cardiopulmonary disorders, diabetes, renal failure, asthma) or who are residents of long-term care facilities

• Women who are pregnant or will be pregnant during influenza season

• People who wish to avoid having influenza

• Health care practitioners and other people in contact with people at high risk of influenza (eg, employees of long-term care facilities, household members and caregivers of at-risk people)

Influenza vaccine is given annually to maintain antibody titers and allow vaccine modification to compensate for antigenic drift. Vaccine is best given in the fall, so that antibody titers will be high during the winter influenza season (between November and March in the US).

Vaccination (both TIV and LAIV) should be avoided in people who

• Have a severe egg allergy

• Previously had a severe reaction to influenza vaccine

• Developed Guillain-Barre syndrome (GBS) within 6 wk of a previous influenza vaccination (it is not known whether influenza vaccination increases risk of recurrent GBS in patients who have previously had GBS that was not related to influenza vaccination)

• Have had GBS in the previous 6 wk, regardless of cause

• Are < 6 mo old

Antiviral drugs: Although vaccination is the preferred method of prevention, antiviral drugs are also effective. Prophylactic antiviral drugs are indicated when influenza is circulating in the community for patients

• Who have been vaccinated only within the previous 2 wk

• For whom vaccination is contraindicated

• Who are immunocompromised and thus may not respond to vaccination

Antiviral drugs do not impair development of immunity from the vaccine. They can be stopped 2 wk after vaccination. If vaccine cannot be given, antiviral drugs are continued for the duration of the epidemic.

If the circulating influenza types or subtypes are unknown, patients may be treated with either zanamivir alone (in patients for whom it is not contraindicated) or with a combination of rimantadine and oseltamivir.

Avian Influenza

Avian influenza (bird flu) is caused by strains of influenza A that normally infect only wild birds (and sometimes pigs). Infections due to these strains have recently been detected in humans.

Most human infections are caused by strains of avian influenza type H5N1, but H7N7, H7N3, and H9N2 have caused some human infections. Infections with these strains are asymptomatic in wild birds but can cause highly lethal illness in domestic birds.

The first human cases of H5N1 were discovered in Hong Kong in 1997. Spread to humans was contained by culling domestic bird populations. However, in 2003 and 2004, H5N1 infections in humans reappeared, and occasional cases continue to be reported, primarily in Asia and the Middle East. Human infections with other avian influenza strains have also been reported in Asia (H9N2), Canada (H7N3), and the Netherlands (H7N7). Although most cases occurred through exposure to infected birds, some person-to-person transmission probably occurred in the Netherlands and in Asia.

All influenza viruses are capable of rapid genetic change, raising the possibility that avian strains could acquire the ability to spread more easily from person to person via direct mutation or via recombination with human strains in a human or porcine host. Many experts are concerned that if these strains acquire the ability to spread efficiently from person to person, an influenza pandemic could result.

Human infection with avian influenza H5N1 strains can cause severe respiratory symptoms. Mortality was 33% in the 1997 outbreak and has been > 60% in subsequent infections. Infection with the H7 strains most commonly causes conjunctivitis, although in the Netherlands outbreak, a few patients had flu-like symptoms and one patient (of 83) died.

Diagnosis

• RT-PCR

An appropriate clinical syndrome in a patient exposed to a person known to be infected or to birds in an area with an ongoing avian influenza outbreak should prompt consideration of this infection. History of recent travel to regions with ongoing transmission from birds to humans (eg, Egypt, Indonesia, Vietnam) plus exposure to birds or infected people should prompt testing for influenza A by RT-PCR. Culture of the organism should not be attempted.

Suspected and confirmed cases are reported to the Centers for Disease Control and Prevention (CDC).

Treatment

• A neuraminidase inhibitor

Treatment with oseltamivir or zanamivir at usual doses is indicated. The H5N1 virus is resistant to amantadine and rimantadine; resistance to oseltamivir has also been reported.

H1N1 Swine Influenza

H1N1 swine influenza (flu) is caused by a new strain of H1N1 influenza A virus, which genetically is a combination of swine, avian, and human influenza viruses.

Most often, pigs are infected by strains of influenza that are slightly different from those that infect people. These strains very rarely spread to people, and when they do, they very rarely then spread from person to person. The H1N1 swine flu virus is a combination of swine, bird (avian), and human influenza viruses that spreads easily from person to person. The infection is not acquired through ingestion of pork and is acquired very rarely by contact with infected pigs.

In June 2009, the World Health Organization declared H1N1 swine flu a pandemic; it has spread to > 70 countries and to all 50 US states. The majority of the deaths occurred in Mexico. The attack rate and mortality for H1N1 swine flu are higher in young and middle-aged adults and lower in the elderly than they are for seasonal flu. The pandemic entered the post-pandemic period in August 2010.

Symptoms and Signs

Symptoms, signs, and complications resemble those of ordinary influenza (see p.), although nausea, vomiting, and diarrhea may be more common. Symptoms are usually mild, but they can become severe, leading to pneumonia or respiratory failure.

Diagnosis

• Sometimes PCR testing of respiratory samples

Because H1N1 swine flu is the predominant strain of influenza currently circulating worldwide, the diagnosis should be considered in any patient with influenza-like symptoms.

A newly developed PCR test can detect the H1N1 virus in respiratory tract samples (eg, nasopharyngeal swabs, nasal washings, tracheal aspirates). Mildly ill patients do not require testing other than for epidemiologic or surveillance purposes; however, local hospital and public health requirements may vary. Usual rapid antigen detection tests have decreased sensitivity for H1N1 swine flu and generally have little clinical use in diagnosis.

Treatment

• Sometimes a neuraminidase inhibitor

Treatment focuses mainly on symptom relief (eg, acetaminophen or ibuprofen for fever and aches). Antiviral drugs may be used, particularly for high-risk patients (see p.) and those who are seriously

ill. Oseltamivir and zanamivir appear to be effective; they are most effective when started within 48 h after symptom onset. In the US, the FDA has issued Emergency Use Authorizations for the use of oseltamivir in patients < 1 yr old and the use of peramivir, an IV neuraminidase inhibitor, in severely ill hospitalized patients.

Most patients recover fully without taking these drugs.

Prevention

Vaccines for H1N1 infection have been developed. Guidelines for use of these vaccines are similar to those for use of seasonal TIV and LAIV.

Commonsense steps (eg, staying home if influenza-like symptoms develop; thorough, frequent hand washing with soap and water or an alcohol-based hand sanitizer) are recommended to reduce the spread of infection.

Parainfluenza Virus Infections

Parainfluenza viruses include several closely related viruses that cause many respiratory illnesses varying from the common cold to an influenza-like syndrome or pneumonia; croup is the most common severe manifestation. Diagnosis is usually clinical. Treatment is supportive.

The parainfluenza viruses are paramyxoviruses types 1, 2, 3, and 4. They share antigenic cross-reactivity but tend to cause diseases of different severity. Type 4 has antigenic cross-reactivity with mumps and appears to be an uncommon cause of respiratory disease.

Childhood outbreaks of parainfluenza virus infections can occur in nurseries, pediatric wards, and schools. Types 1 and 2 tend to cause epidemics in the autumn, with each serotype occurring in alternate years. Type 3 disease is endemic and infects most children < 1 yr; incidence is increased in the spring.

Parainfluenza viruses can cause repeated infections, but reinfection generally causes milder illness. Thus, in immunocompetent adults, most infections are asymptomatic or mild.

The most common illness in children is an upper respiratory illness with no or low-grade fever.

Parainfluenza type 1 probably causes croup (laryngotracheobronchitis—see p.), primarily in infants aged 6 to 36 mo. Croup begins with common cold symptoms. Later, fever, a barking cough, hoarseness, and stridor develop. Respiratory failure due to upper airway obstruction is a rare but potentially fatal complication.

Parainfluenza virus type 3 may cause pneumonia and bronchiolitis in young infants (see p.). These illnesses are generally indistinguishable from disease caused by respiratory syncytial virus (see below) but are often less severe.

A specific viral diagnosis is unnecessary. Treatment is symptomatic.

Respiratory Syncytial Virus and Human Metapneumovirus Infections

Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) infections cause seasonal lower respiratory tract disease, particularly in infants and young children. Disease may be asymptomatic, mild, or severe, including bronchiolitis and pneumonia. Although diagnosis is usually clinical, laboratory diagnosis is readily available. Treatment is supportive.

RSV is an RNA virus, classified as a pneumovirus. Subgroups A and B have been identified. RSV is ubiquitous; almost all children are infected by age 4 yr. Outbreaks occur annually in winter or early spring. Because the immune response to RSV does not protect against reinfection, the attack rate is about 40% for all exposed people. However, antibody to RSV decreases illness severity. RSV is the most common cause of lower respiratory tract illness in young infants and is responsible for > 100,000 hospitalizations

annually in the US.

hMPV is a similar but separate virus. The seasonal epidemiology of hMPV appears to be similar to that of RSV, but the incidence of infection and illness appears to be substantially lower.

Symptoms and Signs

The most recognizable clinical syndromes are bronchiolitis (see p. 2878) and pneumonia. These illnesses typically begin with upper respiratory symptoms and fever, then progress over several days to dyspnea, cough, and wheezing. Apnea may be the initial symptom of RSV in infants < 6 mo. In healthy adults and older children, illness is usually mild and may be inapparent or manifested only as an afebrile common cold. However, patients who are elderly or immunocompromised or who have underlying cardiopulmonary disorders may develop severe disease.

RSV and hMPV illness appear to be similar.

Diagnosis

• Clinical evaluation

• Sometimes rapid antigen tests of nasal washings or swabs

RSV (and possibly hMPV) infection is suspected in infants and young children with bronchiolitis or pneumonia during RSV season. Because antiviral treatment is not typically recommended, a specific laboratory diagnosis is unnecessary for patient management. However, a laboratory diagnosis may facilitate hospital infection control by allowing segregation of children infected with the same virus. Rapid antigen tests with high sensitivities for RSV are available for use in children; nasal washings or swabs are used. These tests are insensitive in adults.

Treatment

• Supportive care

Treatment of RSV and hMPV infections is supportive and includes supplemental O_2 and hydration as needed (see Bronchiolitis on p. 2878).

Corticosteroids and bronchodilators are not generally helpful.

Antibiotics are reserved for patients with fever and evidence of pneumonia on chest x-ray (ie, who may have a bacterial superinfection).

Palivizumab (monoclonal antibody to RSV) is not effective for treatment.

Inhaled ribavirin, an antiviral drug with activity against RSV, has little or no efficacy, is potentially toxic to health care practitioners, and is no longer recommended except for infection in severely immunocompromised patients.

Prevention

Contact precautions (eg, hand washing, gloves, isolation) are important, particularly in hospitals.

Passive prophylaxis with palivizumab decreases the frequency of hospitalization in high-risk infants. It is cost-effective only for infants at high risk of hospitalization (ie, those < 2 yr with hemodynamically significant congenital heart disease or chronic lung disease requiring medical treatment in the preceding 6 mo, those who were born at < 29 wk gestation and are < 1 yr old at the start of RSV season, and those who were born at 29 to 32 wk gestation and are < 6 mo at the start of the season). The dose is 15 mg/kg IM. The first dose is given just before the usual onset of the RSV season (early November in North America). Subsequent doses are given at 1-mo intervals for the duration of the RSV season (usually a

total of 5 doses).

Coronaviruses and Severe Acute Respiratory Syndrome

Coronavirus infections in humans most frequently cause common cold symptoms; however, in 2002, a relatively new coronavirus caused an outbreak of severe acute respiratory syndrome (SARS), which was much more severe than other coronavirus infections.

Coronaviruses are enveloped RNA viruses. Coronaviruses 229E and OC43 cause the common cold, and more recently, 2 new serotypes NL63 and HUK1 have also been associated with this syndrome. In late 2002, a relatively new coronavirus (SARS-CoV) caused an outbreak of SARS, an influenza-like illness that occasionally leads to progressively severe respiratory insufficiency.

SARS-CoV was a new human pathogen that was first detected in the Guangdong province of China in November 2002 and subsequently spread to >30 countries. As of mid-July 2003, > 8000 cases had been reported worldwide, with > 800 deaths (about 10% case mortality rate). This outbreak subsided, and no new cases have been identified since 2004.

Diagnosis is made clinically, and treatment is supportive.

Chapter 151. Herpesviruses

Introduction

Eight types of herpesviruses infect humans (see
Table 151-1). After initial infection, all herpesviruses remain latent within specific host cells and may subsequently reactivate or be shed. Herpesviruses do not survive long outside a host; thus, transmission usually requires intimate contact, although varicellazoster virus (VZV) may spread by aerosol. In people with latent infection, the virus can reactivate without causing symptoms; in such cases, asymptomatic people can transmit infection. Epstein-Barr virus (EBV) and human herpesvirus type 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), are tightly linked with cancer.

Drug Treatment of Herpesviruses

Drugs that have activity against herpesviruses include acyclovir, cidofovir, famciclovir, fomivirsen, foscarnet, ganciclovir, idoxuridine, penciclovir, trifluridine, valacyclovir, valganciclovir, and vidarabine (see
Table 151-2).

Chickenpox

(Varicella)

Chickenpox is an acute, systemic, usually childhood infection caused by the varicella-zoster virus (human herpesvirus type 3). It usually begins with mild constitutional symptoms that are followed shortly by skin lesions appearing

[**Table 151-1.** Herpesviruses that Infect Humans]

[**Table 151-2.** Drugs Used to Treat Herpesvirus Infections]

in crops and characterized by macules, papules, vesicles, and crusting. Patients at risk of severe neurologic or other systemic complications (eg, pneumonia) include adults, neonates, and patients who are immunocompromised or have certain underlying medical conditions. Diagnosis is clinical. Those at risk of severe complications receive postexposure prophylaxis with immune globulin and, if disease develops, are treated with antiviral drugs (eg, valacyclovir, famciclovir, acyclovir). Vaccination provides effective prevention.

Chickenpox is caused by the varicella-zoster virus (human herpesvirus type 3); chickenpox is the acute invasive phase of the virus, and herpes zoster (shingles) represents reactivation of the latent phase (see p.). Chickenpox, which is extremely contagious, is spread by infected droplets and is most communicable during the prodrome and early stages of the eruption. It is communicable from 48 h before the first skin lesions appear until the final lesions have crusted. Indirect transmission (by immune carriers) does not occur.

Epidemics occur in winter and early spring in 3- to 4-yr cycles. Some infants may have partial immunity, probably acquired transplacentally, until age 6 mo.

Symptoms and Signs

In immunocompetent children, chickenpox is rarely severe. In adults and immunocompromised children, infection can be serious. Mild headache, moderate fever, and malaise may occur 11 to 15 days after exposure, about 24 to 36 h before lesions appear. This prodrome is more likely in patients > 10 yr and is usually more severe in adults.

The initial rash, a macular eruption, may be accompanied by an evanescent flush. Within a few hours, lesions progress to papules and then characteristic, sometimes pathognomonic teardrop vesicles, often intensely itchy, on red bases. The lesions become pustular and then crust. Lesions initially develop on the face and trunk and erupt in successive crops; some macules appear just as earlier crops begin to crust.

The eruption may be generalized (in severe cases) or more limited but almost always involves the upper trunk. Ulcerated lesions may develop on the mucous membranes, including the oropharynx and upper respiratory tract, palpebral conjunctiva, and rectal and vaginal mucosa. In the mouth, vesicles rupture immediately, are indistinguishable from those of herpetic gingivostomatitis, and often cause pain during swallowing. Scalp lesions may result in tender, enlarged suboccipital and posterior cervical lymph nodes. New lesions usually cease to appear by the 5th day, and the majority are crusted by the 6th day; most crusts disappear < 20 days after onset.

Complications: Secondary bacterial infection (typically streptococcal or staphylococcal) of the vesicles may occur, causing cellulitis or rarely streptococcal toxic shock. Pneumonia may complicate severe chickenpox in adults, neonates, and immunocompromised patients of all ages but usually not in immunocompetent young children. Myocarditis, transient arthritis or hepatitis, and hemorrhagic complications may also occur.

Encephalopathy occurs in < 1/1000 cases, usually as the disease resolves or within the next 2 wk. Complete neurologic recovery is likely, although rarely, persistent deficits or death occurs. One of the most common neurologic complications is acute postinfectious cerebellar ataxia. Transverse myelitis, cranial nerve palsies, and multiple sclerosis-like clinical manifestations have also occurred. Reye's syndrome (see p.), a rare but severe childhood complication, may begin 3 to 8 days after onset of the rash; aspirin increases the risk. In adults, encephalitis, which can be life threatening, occurs in 1 to 2/1000 cases of chickenpox.

Diagnosis

• Clinical evaluation

Chickenpox is suspected in patients with the characteristic rash, which is usually the basis for diagnosis. The rash may be confused with that of other viral skin infections. If the diagnosis is in doubt, laboratory confirmation can be done; it requires immunofluorescent detection of viral antigen in lesions or culture or serologic findings. Samples are generally obtained with scraping and transported to the laboratory in viral media.

Prognosis

Chickenpox in children is rarely severe. Severe or fatal disease is more likely in adults, patients with depressed T-cell immunity (eg, lymphoreticular cancer), and those receiving corticosteroids or chemotherapy.

Treatment

• Symptomatic treatment

• Valacyclovir or famciclovir for patients ≥ 12 yr, immunocompromised patients, and others at risk of severe disease

Mild cases require only symptomatic treatment. Relief of itching and prevention of scratching, which predisposes to secondary bacterial infection, may be difficult. Wet compresses or, for severe itching, systemic antihistamines and colloidal oatmeal baths may help. Simultaneous use of large doses of systemic and topical antihistamines can cause encephalopathy and should be avoided.

To prevent secondary bacterial infection, patients should bathe regularly and keep their underclothing and hands clean and their nails clipped. Antiseptics should not be applied unless lesions become infected; infection is treated with antibiotics.

Oral antivirals, when given to immunocompetent patients within 24 h of the rash's onset, slightly decrease symptom duration and severity. However, because the disease is generally benign in children, antiviral treatment is not routinely recommended. Oral valacyclovir, famciclovir, or acyclovir should be strongly considered for immunocompromised patients and for healthy people at risk of moderate to severe

disease, including all patients ≥ 12 yr, those with skin disorders (particularly eczema) or chronic lung disease, and those receiving corticosteroid therapy. The dose is famciclovir 500 mg tid or valacyclovir 1 g tid. Acyclovir is a less desirable choice because it has poorer oral bioavailability, but it can be given at 20 mg/kg qid with a maximum daily dose of 3200 mg. Immunocompromised children > 1 yr should be given 500 mg/m^2 q 8 h.

Patients should not return to school or work until the final lesions have crusted.

Prevention

Infection provides lifelong protection. Potentially susceptible people should take strict precautions to avoid people capable of transmitting the infection.

Vaccination: All healthy children and susceptible adults should receive 2 doses of live-attenuated varicella vaccine (see Table 268-10 on p. 2718). Vaccination is particularly important for women of child-bearing age and adults with underlying chronic medical conditions. Serologic testing to determine immune status before vaccination in adults is usually not required. Although the vaccine may cause chickenpox in immunocompetent patients, disease is usually mild (< 10 papules or vesicles) and brief and causes few systemic symptoms.

Vaccination is contraindicated in

• Patients with moderate to severe concurrent illness

• Immunocompromised patients

• Pregnant women

• Patients taking high doses of systemic corticosteroids

• Children using salicylates

Postexposure prophylaxis: After exposure, chickenpox can be prevented or attenuated by IM administration of varicella-zoster immune globulin, which is available as an investigational new drug from FFF Enterprises (800-843-7477). Candidates for postexposure prophylaxis include people with leukemia, immunodeficiencies, or other severe debilitating illness; susceptible pregnant women; and neonates whose mother developed chickenpox within 5 days before or 2 days after delivery. The immune globulin should be given within 4 days of exposure and may modify or prevent varicella. Vaccination should be given as soon as possible in susceptible healthy patients eligible for vaccination, and vaccination can be effective in preventing or ameliorating disease within 3 days and possibly up to 5 days after exposure.

Cytomegalovirus Infection

(Cytomegalic Inclusion Disease)

(See also Congenital and Perinatal Cytomegalovirus Infection on p. 2811.)

Cytomegalovirus (CMV) can cause infections that have a wide range of severity. A syndrome that is similar to infectious mononucleosis but lacks severe pharyngitis is common. Severe focal disease, including retinitis, can develop in HIV-infected patients and, rarely, in organ transplant recipients and other immunocompromised patients. Severe systemic disease can develop in neonates and immunocompromised patients. Laboratory diagnosis, helpful for severe disease, may involve culture, serologic testing, biopsy, or antigen or nucleic acid detection. Ganciclovir and other antiviral drugs are used to treat severe disease, particularly retinitis.

CMV (human herpesvirus type 5) is transmitted through blood, body fluids, or transplanted organs.

Infection may be acquired transplacentally or during birth. Prevalence increases with age; 60 to 90% of adults have had CMV infection. Lower socioeconomic groups tend to have a higher prevalence.

Congenital infection (see p.) may be asymptomatic or may cause abortion, stillbirth, or postnatal death. Complications include extensive hepatic or CNS damage.

Acquired infections are often asymptomatic. An acute febrile illness, termed CMV mononucleosis or CMV hepatitis, may cause hepatitis with elevated aminotransferases, atypical lymphocytosis similar to infectious (Epstein-Barr virus [EBV]) mononucleosis, and splenomegaly.

Postperfusion/posttransfusion syndrome can develop 2 to 4 wk after transfusion with blood products containing CMV. It causes fever lasting 2 to 3 wk and manifestations similar to CMV hepatitis.

In immunocompromised patients, CMV is a major cause of morbidity and mortality. Disease often results from reactivation of latent virus. The lungs, GI tract, or CNS may be involved. In the terminal phase of AIDS, CMV infection causes retinitis in up to 40% of patients and causes funduscopically visible retinal abnormalities. Ulcerative disease of the colon (with abdominal pain and GI bleeding) or of the esophagus (with odynophagia) may occur.

Diagnosis

• Usually clinical evaluation

• Urine culture in infants

• Often biopsy in immunocompromised patients

CMV infection is suspected in healthy people with mononucleosis-like syndromes; immunocompromised patients with GI, CNS, or retinal symptoms; and neonates with systemic disease.

CMV mononucleosis can sometimes be differentiated from infectious (EBV) mononucleosis by the absence of pharyngitis, a negative heterophil antibody test, and serologic testing. CMV infection can be differentiated from viral hepatitis by hepatitis serologic testing. Laboratory confirmation of primary CMV infection is necessary only to differentiate it from other, particularly treatable, conditions or serious disease.

Seroconversion can be demonstrated by development of CMV antibodies and indicates new CMV infection. However, much CMV disease occurs from reactivation of latent disease in the immunocompromised host. Reactivation of CMV can result in virus in the urine, other body fluids, or tissues but does not always indicate disease and may merely represent shedding. Therefore, biopsy showing CMV-induced abnormalities is often necessary to demonstrate invasive disease. Quantitative detection of CMV antigen or DNA in the peripheral blood can also be very helpful because elevated or rising CMV titers are often highly suggestive of invasive disease. Diagnosis in infants can be made by urine culture.

Treatment

• For serious disease, antivirals (eg, ganciclovir, valganciclovir, foscarnet, cidofovir)

Retinitis: CMV retinitis (see p.), which occurs mostly in AIDS patients, is treated with antivirals.

Most patients receive induction therapy with either ganciclovir 5 mg/kg IV bid for 2 to 3 wk or valganciclovir 900 mg po bid for 21 days. If induction fails more than once, another drug should be used. After induction, patients receive maintenance or suppressive therapy with valganciclovir 900 mg po once/day to delay progression. Maintenance therapy with ganciclovir 5 mg/kg IV once/day can also be used to prevent recurrence. Alternatively, foscarnet can be given with or without ganciclovir. Foscarnet 90 mg/kg IV q 12 h for 2 to 3 wk is used for induction, followed by 90 to 120 mg/kg IV once/day for

maintenance therapy. Adverse effects of IV foscarnet are significant and include nephrotoxicity, symptomatic hypocalcemia, hypomagnesemia, hyperphosphatemia, hypokalemia, and CNS effects. Combination therapy with ganciclovir and foscarnet increases efficacy as well as adverse effects.

Cidofovir therapy consists of 5 mg/kg IV once/wk (induction) for 2 wk, followed by a similar dose every other week for maintenance. Efficacy is similar to ganciclovir or foscarnet. Significant adverse effects, including renal failure, limit its use. Cidofovir may cause iritis or ocular hypotony. The potential for nephrotoxicity can be reduced by giving probenecid and prehydration with each dose. However, the adverse effects of probenecid, including rash, headache, and fever, may be significant enough to prevent its use.

Ganciclovir ocular implants can be used for prolonged treatment in some patients. Intraocular injections into the vitreous are given sometimes, primarily if other measures have failed or are contraindicated (salvage therapy). Such treatments include injection of ganciclovir or foscarnet. Potential adverse effects of ocular injection therapy include direct retinal toxicity, vitreous hemorrhage, endophthalmitis, retinal detachment, cystoid macular edema, and cataract formation.

Even patients receiving ocular injections and those with implants need systemic therapy to prevent CMV in the contralateral eye and extraocular tissues. Ultimately, improvement of CD4+ count to > 200 cells/µL with systemic retroviral therapy should prevent the need for ocular implants and chemoprophylaxis.

Other CMV infections: Anti-CMV drugs are used to treat severe disease other than retinitis but are less consistently effective than in retinitis. Ganciclovir plus immune globulin has been used to treat CMV pneumonia in bone marrow transplant recipients.

Prevention

Prophylaxis of CMV disease is necessary for solid organ or hematopoietic cell transplant recipients at risk of CMV disease. Drugs used include ganciclovir, valganciclovir, and valacyclovir.

Herpes Simplex Virus Infections

Herpes simplex viruses (human herpesviruses 1 and 2) commonly cause recurrent infection affecting the skin, mouth, lips, eyes, and genitals. Common severe infections include encephalitis, meningitis, neonatal herpes, and, in immunocompromised patients, disseminated infection. Mucocutaneous infections cause clusters of small painful vesicles on an erythematous base. Diagnosis is clinical; laboratory confirmation by culture, PCR, direct immunofluorescence, or serologic testing can be done. Treatment is symptomatic; antiviral therapy with acyclovir, valacyclovir, or famciclovir is helpful for severe infections and, if begun early, for recurrent or primary infections.

Both types of herpes simplex virus (HSV), HSV-1 and HSV-2, can cause oral or genital infection. Most often, HSV-1 causes gingivostomatitis, herpes labialis, and herpes keratitis. HSV-2 usually causes genital lesions. Transmission of HSV results from close contact with a person who is actively shedding virus. Viral shedding generally occurs from lesions but can occur even when lesions are not apparent.

After the initial infection, HSV remains dormant in nerve ganglia, from which it can periodically emerge, causing symptoms. Recurrent herpetic eruptions are precipitated by overexposure to sunlight, febrile illnesses, physical or emotional stress, immunosuppression, or unknown stimuli. Generally, recurrent eruptions are less severe and occur less frequently over time.

Diseases Caused by Herpes Simplex

Diseases include

• Mucocutaneous infection (most common)

• Ocular infection (herpes keratitis)

• CNS infection

• Neonatal herpes

HSV rarely causes fulminant hepatitis in the absence of cutaneous lesions. In patients with HIV infection, herpetic infections can be particularly severe. Progressive and persistent esophagitis, colitis, perianal ulcers, pneumonia, encephalitis, and meningitis may occur.

HSV outbreaks may be followed by erythema multiforme (see p.), possibly caused by an immune reaction to the virus. Eczema herpeticum (see p.) is a complication of HSV infection in which severe disease develops in skin regions with eczema.

Mucocutaneous infection: Lesions may appear anywhere on the skin or mucosa but are most frequent around or in the mouth or on the lips, conjunctiva and cornea, and genitals. Generally, after a prodromal period (typically < 6 h in recurrent HSV-1) of tingling discomfort or itching, clusters of small, tense vesicles appear on an erythematous base. Clusters vary in size from 0.5 to 1.5 cm but may coalesce. Lesions on the nose, ears, eyes, fingers, or genitals may be particularly painful. Vesicles typically persist for a few days, then rupture and dry, forming a thin, yellowish crust. Healing generally occurs 8 to 12 days after onset. Lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring. Skin lesions can develop secondary bacterial infection. In patients with depressed cell-mediated immunity due to HIV infection or other conditions, prolonged or progressive lesions may persist for weeks or longer. Localized infections can disseminate, particularly—and often dramatically—in immunocompromised patients.

Acute herpetic gingivostomatitis usually results from primary infection with HSV-1, typically in children. Occasionally, through oral-genital contact, the cause is HSV-2. Intraoral and gingival vesicles rupture, usually within several hours to 1 or 2 days, to form ulcers. Fever and pain often occur. Difficulty eating and drinking may lead to dehydration. After resolution, the virus resides dormant in the semilunar ganglion.

Herpes labialis is usually a secondary outbreak of HSV. It develops as ulcers (cold sores) on the vermilion border of the lip or, much less commonly, as ulcerations of the mucosa of the hard palate.

Herpetic whitlow, a swollen, painful, erythematous lesion of the distal phalanx (see p.), results from inoculation of HSV through the skin and is most common among health care practitioners.

Genital herpes is the most common ulcerative sexually transmitted disease in developed countries. It is usually caused by HSV-2, although 10 to 30% of cases involve HSV-1. Primary lesions develop 4 to 7 days after contact. The vesicles usually erode to form ulcers that may coalesce. Lesions may occur on the prepuce, glans penis, and penile shaft in men and on the labia, clitoris, perineum, vagina, and cervix in women. They may occur around the anus and in the rectum in men or women who engage in receptive rectal intercourse. Genital HSV infection may cause urinary hesitancy, dysuria, urinary retention, or constipation. Severe sacral neuralgia may occur. Scarring may follow healing, and recurrences occur in 80% of patients with HSV-2 and in 50% with HSV-1. Primary genital lesions are usually more painful, prolonged, and widespread and are more likely to be bilateral and involve regional adenopathy and constitutional symptoms than recurrent genital lesions. Recurrent lesions may have severe prodromal symptoms and may involve the buttock, groin, or thigh.

Herpes simplex keratitis: HSV infection of the corneal epithelium causes pain, tearing, photophobia, and corneal ulcers that often have a branching pattern (see p.).

Neonatal herpes simplex: Infection develops in neonates, including those whose mothers have no suggestion of current or past herpes infection. It is most commonly transmitted during birth through contact with vaginal secretions containing HSV and usually involves HSV-2. It usually develops between the 1st and 4th wk of life, often causing mucocutaneous vesicles or CNS involvement. It causes major morbidity and mortality (see p.).

CNS infection: Herpes encephalitis (see also p.) occurs sporadically and may be severe. Multiple early seizures are characteristic.

Aseptic meningitis (see p.
) may result from HSV-2. It is usually self-limited and may involve lumbosacral myeloradiculitis, which may cause urinary retention or obstipation.

Diagnosis

• Clinical evaluation

• Viral culture for serious disease

• PCR of CSF and MRI for HSV encephalitis

Diagnosis is often clinical based on characteristic lesions. Laboratory confirmation can be helpful, especially if infection is severe, the patient is immunocompromised or pregnant, or lesions are atypical. A Tzanck test (a superficial scraping from the base of a freshly ruptured vesicle stained with Wright's-Giemsa stain) often reveals multinucleate giant cells in HSV or varicella-zoster virus infection. Definitive diagnosis is with culture, seroconversion involving the appropriate serotype (in primary infections), and biopsy. Fluid and material for culture should be obtained from the base of a vesicle or of a freshly ulcerated lesion. HSV can sometimes be identified using direct immunofluorescence assay of scrapings of lesions. PCR of CSF and MRI are used to diagnose HSV encephalitis.

HSV should be distinguished from herpes zoster, which rarely recurs and usually causes more severe pain and larger groups of lesions that are distributed along a dermatome. Clusters of vesicles or ulcers on an erythematous base are unusual in genital ulcers other than herpes.

If herpes infections recur frequently, do not resolve, or do not respond to antiviral drugs as expected, immunocompromise, possibly due to HIV infection, should be suspected.

Treatment

• Usually acyclovir, valacyclovir, or famciclovir

• For keratitis, topical idoxuridine or trifluridine

Mucocutaneous infection: Isolated infections often go untreated without consequence. Acyclovir, valacyclovir, or famciclovir can be used to treat infection, especially when it is primary. Infection with acyclovir-resistant HSV is rare and occurs almost exclusively in immunocompromised patients. Foscarnet may be effective for acyclovir-resistant infections. Secondary bacterial infections are treated with topical antibiotics (eg, mupirocin or neomycin-bacitracin) or, if severe, with systemic antibiotics (eg, penicillinase-resistant β-lactams). All mucocutaneous herpes infections are treated symptomatically. Systemic analgesics may help.

Gingivostomatitis typically requires only symptom relief with topical anesthetics applied directly with a swab (eg, dyclonine 0.5% liquid or benzocaine 2 to 20% ointment q 2 h as needed). When many large areas are affected, 5% lidocaine viscous may be used as a mouth rinse 5 min before mealtime. (NOTE: Lidocaine must not be swallowed because it anesthetizes the oropharynx, hypopharynx, and possibly the epiglottis. Children must be watched for signs of aspiration.) Severe cases can be treated with acyclovir, valacyclovir, or famciclovir.

Herpes labialis responds to oral and topical acyclovir. The duration of a recurrent eruption may be decreased by about a day by applying penciclovir 1% cream q 2 h while awake for 4 days, beginning during the prodrome or when the first lesion appears. Toxicity appears to be minimal. Famciclovir 1500 mg as one dose or valacyclovir 2 g po q 12 h for 1 day can be used to treat recurrent herpes labialis. Acyclovir-resistant strains are resistant to penciclovir. Docosanol 10% cream may be effective when used 5 times/day.

Genital herpes is treated with antiviral drugs. Acyclovir 200 mg po 5 times/day for 10 days, valacyclovir 1 g po bid for 10 days, or famciclovir 250 mg po tid for 7 to 10 days can be used for primary eruptions. These drugs reduce viral shedding and symptoms in severe primary infections. However, even early treatment of primary infections does not prevent recurrences.

In recurrent eruptions, symptom duration and severity can be reduced marginally by antiviral treatment, particularly during the prodromal phase. Acyclovir 200 mg po q 4 h for 5 days, valacyclovir 500 mg po bid for 3 days, or famciclovir 1000 mg po bid for 1 day can be used. Patients with frequent eruptions (eg, > 6 eruptions/yr) may receive suppressive antiviral therapy with acyclovir 400 mg po bid, valacyclovir 500 to 1000 mg po once/day, or famciclovir 250 mg po bid. Doses should be adjusted for renal insufficiency. Adverse effects are infrequent with oral administration but may include nausea, vomiting, diarrhea, headache, and rash.

Herpes simplex keratitis: Treatment involves topical antivirals, such as idoxuridine or trifluridine, and should be supervised by an ophthalmologist (see p.).

Neonatal herpes simplex: Acyclovir 20 mg/kg IV q 8 h for 14 to 21 days should be used. A dose of 20 mg/kg IV q 8 h for 21 days is indicated for CNS and disseminated HSV disease.

CNS infection: Encephalitis is treated with acyclovir 10 mg/kg IV q 8 h for 14 to 21 days. Up to 20 mg/kg IV q 8 h can be used in children. Aseptic meningitis is usually treated with IV acyclovir. Acyclovir is generally very well tolerated. However, adverse effects can include phlebitis, renal dysfunction, and, rarely, neurotoxicity (lethargy, confusion, seizures, coma).

Herpes Zoster

(Shingles; Acute Posterior Ganglionitis)

Herpes zoster is infection that results when varicella-zoster virus reactivates from its latent state in a posterior dorsal root ganglion. Symptoms usually begin with pain along the affected dermatome, followed in 2 to 3 days by a vesicular eruption that is usually diagnostic. Treatment is antiviral drugs and possibly corticosteroids given within 72 h after skin lesions appear.

Chickenpox and herpes zoster are caused by the varicella-zoster virus (human herpesvirus type 3); chickenpox is the acute invasive phase of the virus (see p.), and herpes zoster (shingles) represents reactivation of the latent phase. Herpes zoster inflames the sensory root ganglia, the skin of the associated dermatome, and sometimes the posterior and anterior horns of the gray matter, meninges, and dorsal and ventral roots. Herpes zoster frequently occurs in elderly and HIV-infected patients and is more severe in immunocompromised patients. There are no clear-cut precipitants.

Symptoms and Signs

Lancinating, dysesthetic, or other pain develops in the involved site, followed in 2 to 3 days by a rash, usually crops of vesicles on an erythematous base. The site is usually one or more adjacent dermatomes in the thoracic or lumbar region. Lesions are typically unilateral. The site is usually hyperesthetic, and pain may be severe. Lesions usually continue to form for about 3 to 5 days. Herpes zoster may disseminate to other regions of the skin and to visceral organs, especially in immunocompromised patients.

Fewer than 4% of patients with herpes zoster experience another outbreak. However, many, particularly the elderly, have persistent or recurrent pain in the involved distribution (postherpetic neuralgia), which may persist for months, years, or permanently. Infection in the trigeminal nerve is particularly likely to lead to severe, persistent pain. The pain of postherpetic neuralgia may be sharp and intermittent or constant and may be debilitating.

Geniculate zoster (Ramsay Hunt syndrome) results from involvement of the geniculate ganglion. Ear pain, facial paralysis, and sometimes vertigo occur. Vesicles erupt in the external auditory canal, and taste

may be lost in the anterior two thirds of the tongue (see also Herpes Zoster Oticus on p. 444).

Ophthalmic herpes zoster (see also p. 590) results from involvement of the gasserian ganglion, with pain and vesicular eruption in and around the eye, in the distribution of the ophthalmic division of the 5th cranial nerve. Vesicles on the tip of the nose (Hutchinson's sign) indicate involvement of the nasociliary branch and often severe ocular disease. However, eye involvement may occur in the absence of lesions on the tip of the nose.

Intraoral zoster is uncommon but may produce a sharp unilateral distribution of lesions. No intraoral prodromal symptoms occur.

Diagnosis

• Clinical evaluation

Herpes zoster is suspected in patients with the characteristic rash and sometimes in patients with typical pain in a dermatomal distribution. Diagnosis is usually based on the virtually pathognomonic rash. If the diagnosis is equivocal, detecting multinucleate giant cells with a Tzanck test can confirm infection, but the Tzanck test is positive with herpes zoster or herpes simplex. Herpes simplex virus (HSV) may cause nearly identical lesions, but unlike herpes zoster, HSV tends to recur and is not dermatomal. Viruses can be differentiated by culture. Antigen detection from a biopsy sample can be useful.

Treatment

• Symptomatic treatment

• Antivirals (acyclovir, famciclovir, valacyclovir) for immunocompromised or pregnant patients

Wet compresses are soothing, but systemic analgesics are often necessary. Treatment with oral antivirals decreases the severity and duration of the acute eruption, the incidence of postherpetic neuralgia, and the rate of serious complications in immunocompromised patients and pregnant women. Treatment should start as soon as possible, ideally during the prodrome, and is likely to be ineffective if given > 72 h after skin lesions appear. Famciclovir 500 mg po tid for 7 days and valacyclovir 1 g po tid for 7 days have better bioavailability with oral dosing than acyclovir, and therefore for herpes zoster, they are generally preferred to oral acyclovir 800 mg 5 times/day for 7 to 10 days. Corticosteroids moderately increase the rate of healing and resolution of acute pain but do not decrease the incidence of postherpetic neuralgia.

For immunocompromised patients, acyclovir is recommended at a dosage of 10 mg/kg IV q 8 h for 7 days for adults and 20 mg/kg IV q 8 h for 7 days for children < 12 yr.

Management of postherpetic neuralgia can be particularly difficult. Treatments include gabapentin, cyclic antidepressants, and topical capsaicin or lidocaine ointment. Opioid analgesics may be necessary. Intrathecal methylprednisolone may be of benefit.

For treatment of ophthalmic herpes zoster, an ophthalmologist should be consulted (see p. 591). For treatment of otic herpes zoster, an otolaryngologist should be consulted (see p. 445).

Prevention

Prevention involves preventing primary infection (chickenpox) by giving the varicella vaccine (see p. 1416) to children and susceptible adults. Adults ≥ 60 yr should have a single dose of zoster vaccine (a more potent preparation of varicella vaccine) whether they have had herpes zoster or not. This vaccine has been shown to decrease the incidence of zoster.

Infectious Mononucleosis

Infectious mononucleosis is caused by Epstein-Barr virus (EBV, human herpesvirus type 4), characterized by fatigue, fever, pharyngitis, and lymphadenopathy. Fatigue may persist weeks

or months. Severe complications, including splenic rupture and neurologic syndromes, occasionally occur. Diagnosis is clinical or with EBV serologic testing. Treatment is supportive.

EBV is a herpesvirus that infects 50% of children before age 5. Its host is humans.

Pathophysiology

After initial replication in the nasopharynx, the virus infects B cells, which are induced to secrete immunoglobulins, including heterophil antibodies. Morphologically abnormal (atypical) lymphocytes develop, mainly from CD8+ T cells.

After primary infection, EBV remains within the host, primarily in B cells, for life and undergoes intermittent asymptomatic shedding from the oropharynx. The virus is detectable in oropharyngeal secretions of 15 to 25% of healthy EBV-seropositive adults. Shedding increases in frequency and titer in immunocompromised patients (eg, organ allograft recipients, HIV-infected people).

EBV has not been recovered from environmental sources and is not very contagious. Transmission may occur via transfusion of blood products but much more frequently occurs via kissing between an uninfected and an EBV-seropositive person who is shedding the virus asymptomatically. Only about 5% of patients acquire EBV from someone who has acute infection. Early childhood transmission occurs more frequently among lower socioeconomic groups and in crowded conditions.

Complications: EBV is statistically associated with and likely has a causal role in Burkitt's lymphoma, certain B-cell tumors in immunocompromised patients, and nasopharyngeal carcinoma. EBV does not cause chronic fatigue syndrome. However, it may occasionally cause a syndrome of fever, interstitial pneumonitis, pancytopenia, and uveitis (ie, chronic active EBV).

Symptoms and Signs

In most young children, primary EBV infection is asymptomatic. Symptoms of infectious mononucleosis develop most often in older children and adults.

The incubation period is about 30 to 50 days. The triad of fever, pharyngitis, and adenopathy is present in most patients. Fatigue can last months but is usually maximal during the first 2 to 3 wk. Fever usually peaks in the afternoon or early evening, with a temperature around 39.5° C, although it may reach 40.5° C. Pharyngitis may be severe, painful, and exudative and may resemble streptococcal pharyngitis. Adenopathy is usually symmetric and may involve any group of nodes, particularly the anterior and posterior cervical chains. Adenopathy may be the only manifestation.

Splenomegaly, which occurs in about 50% of cases, is maximal during the 2nd and 3rd wk and usually results in only a barely palpable splenic tip. Mild hepatomegaly and hepatic percussion tenderness may occur. Patients may have periorbital edema and palatal petechiae. Less frequent findings include maculopapular eruptions and jaundice.

Complications: Although recovery is usually complete, complications may be dramatic.

Neurologic complications are rare but may include encephalitis, seizures, Guillain-Barre syndrome, peripheral neuropathy, aseptic meningitis, myelitis, cranial nerve palsies, and psychosis. Encephalitis may manifest with cerebellar dysfunction, or it may be global and rapidly progressive, similar to herpes simplex encephalitis, but is usually self-limited.

Hematologic complications are usually self-limited. They include granulocytopenia, thrombocytopenia, and hemolytic anemia. Transient mild granulocytopenia or thrombocytopenia occurs in about 50% of patients; severe cases, associated with bacterial infection or bleeding, occur less frequently. Hemolytic anemia is often due to anti-i-specific antibodies.

Splenic rupture can have severe consequences. It can result from splenic enlargement and capsular swelling, which are maximal 10 to 21 days after presentation. A history of trauma is present only about

half of the time. Rupture is usually painful but occasionally causes painless hypotension. Treatment is discussed on p. 986.

Respiratory complications include, rarely, upper airway obstruction due to pharyngeal or paratracheal lymphadenopathy; respiratory complications may respond to corticosteroids. Clinically silent interstitial pulmonary infiltrates occur mostly in children and are usually visible on x-rays.

Hepatic complications include elevated aminotransferase levels (about 2 to 3 times normal, returning to baseline over 3 to 4 wk); they occur in about 95% of patients. If jaundice or more severe enzyme elevations occur, other causes of hepatitis should be investigated.

Overwhelming infection with EBV occurs sporadically but may cluster in families, particularly those with X-linked lymphoproliferative syndrome (see also p. 1108). Survivors of overwhelming primary EBV infection are at risk of developing agammaglobulinemia or lymphoma.

Diagnosis

• Heterophil antibody test

• Sometimes EBV serologic testing

Infectious mononucleosis should be suspected in patients with typical symptoms and signs. Exudative pharyngitis, anterior cervical lymphadenopathy, and fever may be clinically indistinguishable from those caused by group A β-hemolytic streptococci. However, posterior cervical or generalized adenopathy or hepatosplenomegaly suggests infectious mononucleosis. Moreover, detection of streptococci in the oropharynx does not exclude infectious mononucleosis.

Primary HIV infection (see p. 1438) can produce a clinical picture resembling acute EBV infection. If patients have risk factors for HIV infection, quantitative HIV RNA viral blood count, p24 antigen assay, and CD4 count, plus EBV serologic testing, should be done. HIV enzyme-linked immunosorbent assay (ELISA)/Western blot is usually negative during the acute infection and thus is not useful in early primary HIV infection.

Cytomegalovirus (CMV) may cause a syndrome similar to infectious mononucleosis, with atypical lymphocytosis as well as hepatosplenomegaly and hepatitis but usually not with severe pharyngitis. Toxoplasmosis, hepatitis B, rubella, or atypical lymphocytes associated with adverse drug reactions can also cause infectious mononucleosis-like syndromes. These syndromes can usually be distinguished by their other clinical features or by specific testing.

Laboratory diagnosis usually involves a CBC and EBV serologic testing. Lymphocytes that are morphologically atypical account for up to 80% of the WBCs. Although individual lymphocytes may resemble leukemic lymphocytes, lymphocytes are heterogeneous, which is unlikely in leukemia. Atypical lymphocytes may also be present in HIV or CMV infection, hepatitis B, influenza B, rubella, or other viral illnesses, so diagnosis requires serologic testing. However, very high atypical lymphocyte counts are typically seen only in primary EBV and CMV infection. Two serologic tests are used to diagnose acute EBV infection: heterophil antibody testing and specific EBV antibody testing.

Heterophil antibodies are measured using various card-agglutination (monospot) tests. However, heterophil antibodies are present in only 50% of patients < 5 yr and in about 80 to 90% of adolescents and adults. Importantly, the heterophil antibody test may be false-positive in some patients with acute HIV infection. The titer and prevalence of heterophil antibodies rise during the 2nd and 3rd wk of illness. Thus, if the diagnosis is strongly suspected but the heterophil antibody test is negative, repeating the test after 7 to 10 days of symptoms is reasonable. If the test remains negative, antibodies to EBV should be measured. The presence of IgM antibodies to the EBV viral capsid antigen (VCA) indicates primary EBV infection (these antibodies disappear within 3 mo after infection). EBV VCA-IgG antibodies develop later (perhaps after 8 wk) in acute EBV infection and persist for life. If EBV antibody titers are negative or indicate remote infection (ie, positive for IgG antibodies and negative for IgM antibodies), other diagnoses (eg, acute HIV infection, CMV infection) should be considered.

Prognosis

Infectious mononucleosis is usually self-limited. Duration of illness varies; the acute phase lasts about 2 wk. Generally, 20% of patients can return to school or work within 1 wk, and 50% within 2 wk. Fatigue may persist for several more weeks or, in 1 to 2% of cases, for months. Death occurs in < 1%, mostly resulting from complications (eg, encephalitis, splenic rupture, airway obstruction).

Treatment

• Supportive care

• Corticosteroids possibly helpful for severe disease

Treatment is supportive. Patients are encouraged to rest during the acute phase but can resume activity when fever, pharyngitis, and malaise abate. To prevent splenic rupture, patients should avoid heavy lifting and contact sports for 1 mo after presentation and until splenomegaly (which can be monitored by ultrasonography) resolves.

Although corticosteroids hasten defervescence and relieve pharyngitis, they generally should not be used in uncomplicated disease. Corticosteroids can be helpful for complications such as impending airway obstruction, severe thrombocytopenia, and hemolytic anemia. Although oral or IV acyclovir decreases oropharyngeal shedding of EBV, there is no convincing evidence to warrant its clinical use.

Roseola Infantum

(Exanthem Subitum; Pseudorubella)

Roseola infantum is an infection of infants or very young children caused by human herpesvirus 6 (HHV-6) or, less commonly, HHV-7. The infection causes high fever and a rubelliform eruption that occurs during or after defervescence, but localizing symptoms or signs are absent. Diagnosis is clinical, and treatment is symptomatic.

Roseola infantum is the most well-described illness to result from HHV-6. HHV-6 may also cause visceral disease in immunocompromised patients (eg, organ transplant recipients). Roseola infantum occurs most often in the spring and fall. Minor local epidemics have been reported.

Symptoms and Signs

The incubation period is about 5 to 15 days. Fever of 39.5 to 40.5° C begins abruptly and persists 3 to 5 days without any localizing symptoms or signs. Despite the high fever, the child is usually alert and active, although febrile seizures may occur. Cervical and posterior auricular lymphadenopathy often develops. Encephalitis or hepatitis occurs rarely.

The fever usually falls rapidly on the 4th day, and when the fall occurs, a macular or maculopapular exanthem usually appears prominently on the chest and abdomen and, to a lesser extent, on the face and extremities; it lasts for a few hours to 2 days and may be unnoticed in mild cases. In 70% of HHV-6 infections, the classic exanthem does not occur.

Diagnosis

If roseola is known to be in the community, it may be suspected when a child aged 6 mo to 3 yr develops typical symptoms and signs. Testing is rarely needed, but diagnosis can be confirmed by culture, PCR, or serologic tests.

Treatment

Treatment is generally symptomatic. Foscarnet or ganciclovir have been used to treat some

immunosuppressed patients with severe disease, although controlled trials are lacking. Foscarnet is more consistently active than ganciclovir against HHV-6.

Chapter 152. Enteroviruses

Introduction

Enteroviruses include

• Coxsackieviruses A1 to A22, A24, and B1 to 6

• Echoviruses (enteric cytopathic human orphan viruses) 1 to 7, 9, 11 to 21, 24 to 27, and 29 to 33

• Enteroviruses 68 to 71, 73 to 91, and 100 to 101

• Polioviruses types 1 to 3

Enteroviruses, along with rhinoviruses (see Common Cold on p. 1404) and human parechoviruses, are picornaviruses (*pico*, or small, RNA viruses). Human parechoviruses types 1 and 2 were previously named echovirus 22 and 23 but have now been reclassified. All enteroviruses are antigenically heterogeneous and have wide geographic distribution.

Enteroviruses are shed in respiratory secretions and stool and sometimes are present in the blood and CSF of infected patients. Infection is usually transmitted by direct contact with respiratory secretions or stool but can be transmitted by contaminated environmental sources (eg, water). Enteroviral diseases or epidemics in the US occur in summer and fall. Infection transmitted by a mother during delivery can cause severe disseminated neonatal infection, which may include hepatitis or hepatic necrosis, meningoencephalitis, myocarditis, or a combination.

Intact humoral immunity and B-cell function are required for control of enteroviral disease. Severe enteroviral infections (often manifesting as a slowly progressive meningoencephalitis) occur in patients with agammaglobulinemia but usually not in those with other immune deficiencies.

Diseases Caused by Enteroviruses

Enteroviruses cause various syndromes (see Table 152-1). Epidemic pleurodynia, hand-foot-and-mouth disease, herpangina, and poliomyelitis are caused almost exclusively by enteroviruses. Other disorders (eg, aseptic meningitis, myopericarditis) may be caused by enteroviruses or other organisms.

Aseptic meningitis: Aseptic meningitis is most common among infants and children. In infants and young children, the cause is frequently a group A or B coxsackievirus, an echovirus, or a human parechovirus. In older children and adults, other enteroviruses as well as other viruses may cause aseptic meningitis.

[**Table 152-1.** Syndromes Caused by Enteroviruses]

The course is usually benign. A rash may accompany enteroviral aseptic meningitis. Rarely, encephalitis, which may be severe, also occurs.

Although rarely clinically necessary, the causative virus can often be isolated in a sample from the throat, stool, or CSF or be identified by reverse transcriptase-PCR.

Hemorrhagic conjunctivitis: Rarely, this disorder occurs in epidemics in the US. Importation of the virus from Africa, Asia, Mexico, and the Caribbean may make outbreaks more common.

The eyelids rapidly swell. Hemorrhagic conjunctivitis, unlike uncomplicated conjunctivitis, often leads to subconjunctival hemorrhages or keratitis, causing pain, tearing, and photophobia. Systemic illness is uncommon. However, when hemorrhagic conjunctivitis is due to enterovirus 70, transient lumbosacral radiculomyelopathy or poliomyelitis-like illness (with paralysis) can occur but is rare. Recovery is usually complete within 1 to 2 wk of onset.

Coxsackievirus A24 also causes hemorrhagic conjunctivitis, but subconjunctival hemorrhage is less frequent, and neurologic complications have not been described. Most patients recover in 1 to 2 wk.

Myopericarditis: Cardiac infection may occur at any age, but most patients are 20 to 39 yr old. Patients may present with chest pain, arrhythmias, or heart failure. Recovery is usually complete, but some patients develop dilated cardiomyopathy. Diagnosis may require PCR of myocardial tissue.

Myocarditis neonatorum (cardiac infection at birth) is caused by group B coxsackieviruses and some echoviruses. It causes fever and heart failure and has a high mortality rate.

Neonatal infection: Usually, several days after birth, the neonate suddenly develops a syndrome resembling sepsis with fever, lethargy, disseminated intravascular coagulation, bleeding, and multiple organ (including heart) failure. CNS, hepatic, myocardial, pancreatic, or adrenal lesions may occur simultaneously. Recovery may occur within a few weeks, but death may result from circulatory collapse or, if the liver is involved, liver failure.

Rashes: Certain coxsackieviruses and echoviruses may cause rashes, often during epidemics. Rashes are usually nonpruritic, do not desquamate, and occur on the face, neck, chest, and extremities. They are sometimes maculopapular or morbilliform but occasionally hemorrhagic, petechial, or vesicular. Fever is common. Aseptic meningitis may develop simultaneously. The course is usually benign.

Respiratory infections: These infections may result from enteroviruses. Symptoms include fever, coryza, pharyngitis, and, in some infants and children, vomiting and diarrhea. Bronchitis and interstitial pneumonia occasionally occur in adults and children. The course is usually mild.

Diagnosis

Diagnosis of enteroviral diseases is clinical. Laboratory diagnosis is usually unnecessary but can often be made by culturing the virus, by detecting viral RNA using reverse transcriptase-PCR or, less commonly, by demonstrating seroconversion. Enteroviruses that cause aseptic meningitis can be cultured in a sample from the throat, stool, blood, or CSF.

Treatment

Treatment of enteroviral disease is supportive. Patients with agammaglobulinemia are treated with IV immune globulins with variable success.

Epidemic Pleurodynia

(Bornholm Disease)

Epidemic pleurodynia is a febrile disorder caused most commonly by a group B coxsackievirus. Infection causes severe pleuritic chest or abdominal pain.

Epidemic pleurodynia may occur at any age but is most common among children. Severe, frequently intermittent, often pleuritic pain begins suddenly in the epigastrium, abdomen, or lower anterior chest, with fever and often headache, sore throat, and malaise. The involved truncal muscles may become swollen and tender. Symptoms usually subside in 2 to 4 days but may recur within a few days and persist or recur for several weeks. Up to 5% of cases are complicated by aseptic meningitis, orchitis, and, less commonly, myopericarditis. After recovery, subsequent infection with another group B coxsackievirus is possible.

Diagnosis

• Clinical evaluation

Diagnosis may be obvious in a child who has unexplained severe pleuritic or abdominal pain during an epidemic. However, in other situations, symptoms may be hard to distinguish from those due to other

conditions that cause chest or abdominal pain.

Laboratory diagnosis is not routinely necessary; it consists of isolating the virus in a throat or stool culture or, less commonly, demonstrating seroconversion.

Treatment

Treatment includes NSAIDs and other symptomatic measures.

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease is a febrile disorder usually caused by coxsackievirus A16, enterovirus 71, or other enteroviruses. Infection causes a vesicular eruption of skin and mucosa.

The disease is most common among young children. The course is similar to that of herpangina (see below).

Children have a sore throat or mouth pain and may refuse to eat. Fever is common. Vesicles are distributed over the buccal mucosa and tongue, the hands and feet, and, occasionally, the buttocks or genitals; usually, the vesicles are benign and short-lived.

Infection with enterovirus 71 may be accompanied by severe neurologic manifestations (eg, meningitis, encephalitis, polio-like paralysis). Morbidity and mortality are significantly higher with enterovirus 71 than with coxsackievirus A16 or other enteroviruses.

The diagnosis of hand-foot-and-mouth disease is usually made clinically.

Treatment is symptomatic (see p.).

Herpangina

Herpangina is a febrile disorder caused by numerous group A coxsackieviruses and occasionally other enteroviruses. Infection causes oropharyngeal mucosal vesicular and ulcerative lesions.

Herpangina tends to occur in epidemics, most commonly in infants and children. It is characterized by sudden onset of fever with sore throat, headache, anorexia, and frequently neck pain. Infants may vomit. Within 2 days after onset, up to 20 (mean, 4 to 5) 1- to 2-mm diameter grayish papules develop and become vesicles with erythematous areolae. They occur most frequently on the tonsillar pillars but also on the soft palate, tonsils, uvula, or tongue. During the next 24 h, the lesions become shallow ulcers, seldom > 5 mm in diameter, and heal in 1 to 7 days.

Complications are unusual. Lasting immunity to the infecting strain follows, but repeated episodes caused by other group A coxsackieviruses or other enteroviruses are possible.

Diagnosis

• Clinical evaluation

Diagnosis is based on symptoms and characteristic oral lesions. Confirmatory testing is not usually required but can be done by isolating the virus from the lesions, detecting virus by reverse transcriptase-PCR, or by demonstrating a rise in specific antibody titer.

Recurrent aphthous ulcers may appear similar. Rarely, Bednar's aphthous ulcers occur in the pharynx but usually without systemic symptoms. Herpetic stomatitis occurs sporadically and causes larger, more persistent, and more numerous ulcers throughout the oropharynx than herpangina. Coxsackievirus A10 causes lymphonodular pharyngitis, which is similar except that the papules become 2- to 3-mm whitish to

yellowish nodules instead of vesicles and ulcers.

Treatment

Treatment of herpangina is symptomatic (see p.).

Poliomyelitis

(Infantile Paralysis; Acute Anterior Poliomyelitis)

Poliomyelitis is an acute infection caused by a poliovirus. Manifestations include a nonspecific minor illness (abortive poliomyelitis), sometimes aseptic meningitis without paralysis (nonparalytic poliomyelitis), and, less often, flaccid weakness of various muscle groups (paralytic poliomyelitis). Diagnosis is clinical, although laboratory diagnosis is possible. Treatment is supportive.

Polioviruses have 3 serotypes. Type 1 is the most paralytogenic and used to be the most common cause of epidemics. Humans are the only natural host. Infection is highly transmittable via direct contact. Asymptomatic and minor infections (abortive poliomyelitis) are more common than nonparalytic or paralytic infections by ≥ 60:1 and are the main source of spread. Extensive vaccination has almost eradicated the disease in developed countries. However, cases still occur in regions with incomplete immunization, such as sub-Saharan Africa and southern Asia.

Pathophysiology

The virus enters the mouth via the fecal-oral route, then enters the lymphoid tissues of the GI tract. A primary (minor) viremia follows with spread of virus to the reticuloendothelial system. Infection may be contained at this point, or the virus may further multiply and cause several days of secondary viremia, culminating in the development of symptoms and antibodies.

In paralytic infections, poliovirus enters the CNS—whether via secondary viremia or via migration up peripheral nerves is unclear. Significant damage occurs in only the spinal cord and brain, particularly in the nerves controlling motor and autonomic function. Inflammation compounds the damage produced by primary viral invasion. Factors predisposing to serious neurologic damage include increasing age (throughout life), recent tonsillectomy or intramuscular injection, pregnancy, impairment of B-cell function, and physical exertion concurrent with onset of the CNS phase.

Poliovirus is present in the throat and feces during incubation and, after symptom onset, persists 1 to 2 wk in the throat and ≥ 3 to 6 wk in feces; the fecal-oral route is the usual method of transmission.

Symptoms and Signs

Most (90 to 95%) infections cause no symptoms. Symptomatic disease is classified as abortive poliomyelitis or as paralytic or nonparalytic poliomyelitis.

Abortive: Most symptomatic infections, particularly in young children, are minor, with 1 to 3 days of slight fever, malaise, headache, sore throat, and vomiting, which develop 3 to 5 days after exposure. There are no neurologic symptoms or signs, and physical examination is unremarkable except for the presence of fever.

Paralytic and nonparalytic: Paralytic poliomyelitis occurs in about 0.1% of all infections. It may develop without a preceding minor illness, particularly in older children and adults. Incubation is usually 7 to 14 days.

Common manifestations include aseptic meningitis, deep muscle pain, hyperesthesias, paresthesias, and, during active myelitis, urinary retention and muscle spasms. Asymmetric flaccid paralysis may develop and progress over 2 to 3 days. Encephalitic signs occasionally predominate.

Dysphagia, nasal regurgitation, and nasal voice are usually the earliest signs of bulbar involvement, but some patients have pharyngeal paralysis and cannot control oral secretions. As with skeletal muscle paralysis, bulbar involvement may worsen over 2 to 3 days and, in some patients, affects the respiratory and circulatory centers of the brain stem, leading to respiratory compromise. Infrequently, respiratory failure develops when the diaphragm or intercostal muscles are affected.

Some patients develop postpoliomyelitis syndrome (see below).

Diagnosis

• Lumbar puncture

• Viral culture (stool, throat, and CSF)

• Reverse transcriptase-PCR of blood or CSF

• Serologic testing for poliovirus serotypes, enteroviruses, and West Nile virus

When there are no CNS manifestations, symptomatic polio resembles other systemic viral infections and is typically not considered or diagnosed except during an epidemic.

Nonparalytic poliomyelitis resembles other viral meningitides. In such patients, lumbar puncture is usually done; typical CSF findings are normal glucose, mildly elevated protein, and a cell count of 10 to 500/μL (predominantly lymphocytes). Isolation of the virus from the throat, feces, or CSF or demonstration of a rise in specific antibody titer confirms infection with poliovirus but is usually not needed in patients with uncomplicated aseptic meningitis.

Asymmetric flaccid limb paralysis or bulbar palsies without sensory loss during an acute febrile illness in a nonimmunized child or young adult almost always indicates paralytic poliomyelitis. However, certain group A and B coxsackieviruses (especially A7), several echoviruses, and enterovirus type 71 may produce similar findings. West Nile virus infection can also cause an acute flaccid paralysis that is clinically indistinguishable from paralytic poliomyelitis due to polioviruses. Guillain-Barre syndrome (see p.) causes flaccid paralysis but can be distinguished because it usually causes no fever, muscle weakness is symmetric, sensory deficits occur in 70% of patients, and CSF protein is usually elevated and CSF cell count is normal.

Epidemiologic clues (eg, immunization history, recent travel, age, season) can help suggest the cause. Because identification of poliovirus or another enterovirus as the cause of acute flaccid paralysis is important for public health reasons, viral culture of throat swabs, stool, and CSF and reverse transcriptase-PCR of CSF and blood should be done in all cases. Specific serologic testing for polioviruses, other enteroviruses, and West Nile virus should also be done.

Prognosis

In nonparalytic forms, recovery is complete.

In paralytic forms, about two thirds of patients have residual permanent weakness. Bulbar paralysis is more likely to resolve than peripheral paralysis. Mortality is 4 to 6% but increases to 10 to 20% in adults and in patients with bulbar disease.

Postpoliomyelitis syndrome: Muscle fatigue and decreased endurance, often accompanied by weakness, fasciculations, and atrophy, may develop years or decades after paralytic poliomyelitis, particularly in older patients and in patients who are severely affected initially. Damage usually occurs in previously affected muscle groups. The cause may be related to further loss of anterior horn cells due to aging in a population of neurons already depleted by earlier poliovirus infection. However, it rarely substantially increases disability.

Treatment

• Supportive care

Standard treatment is supportive and includes rest, analgesics, and antipyretics as needed. Specific antiviral therapy is not available.

During active myelitis, precautions to avoid complications of bed rest (eg, deep venous thrombosis, atelectasis, UTI) and prolonged immobility (eg, contractures) may be necessary. Respiratory failure may require mechanical ventilation. Mechanical ventilation or bulbar paralysis requires intensive pulmonary toilet measures.

Treatment of postpoliomyelitis syndrome is supportive.

Prevention

All infants and children should be immunized. The American Academy of Pediatrics recommends vaccination at ages 2 mo, 4 mo, and 6 to 18 mo and a booster dose at age 4 to 6 yr (see also p. 1177 and Table 268-10 on p. 2718). Childhood vaccination produces immunity in > 95% of recipients.

Salk inactivated poliovirus vaccine (IPV) is preferred to Sabin live-attenuated oral polio vaccine (OPV), which causes paralytic poliomyelitis in about 1 case per 2,400,000 doses and is thus no longer available in the US. Serious adverse effects have not been associated with IPV.

Adults are not routinely vaccinated. Nonimmunized adults traveling to endemic or epidemic areas should receive primary vaccination with IPV, including 2 doses given 4 to 8 wk apart and a 3rd dose given 6 to 12 mo later. At least 1 dose is given before travel. Immunized adults traveling to endemic or epidemic areas should be given 1 dose of IPV. Immunocompromised hosts and their household contacts should not be given OPV.

Chapter 153. Arboviridae, Arenaviridae, and Filoviridae

Introduction

Arbovirus (arthropod-borne virus) is a term applied to a group of viruses that are transmitted to vertebrates by certain types of blood-eating insects, chiefly mosquitoes and ticks (arthropods). Arbovirus is not part of the current viral classification system. Families in the current classification system that have some arbovirus members include

• Bunyaviridae (including bunyaviruses, phleboviruses, nairoviruses, and hantaviruses)

• Flaviviridae (including flaviviruses)

• Reoviridae (including coltiviruses and orbiviruses)

• Togaviridae (including alphaviruses)

Arenaviridae and Filoviridae (including Marburg and Ebola viruses) are not arboviruses.

Arboviruses number > 250 and are distributed worldwide; at least 80 cause human disease. Birds are often reservoirs for arboviruses, which are transmitted by mosquitoes to horses, other domestic animals, and humans. Most arboviral diseases are not transmissible by humans, perhaps because the typical viremia is inadequate to infect the arthropod vector; an exception is dengue fever, which can be transmitted from person to person via mosquitoes. Some infections (eg, West Nile virus, Colorado tick fever) can be spread by blood transfusion or organ donation. Reservoirs for Bunyaviridae include insects and vertebrates, often rodents. These viruses spread to humans directly from their reservoirs, but human-to-human transmission may occur.

Arenaviruses are usually transmitted by rodents and their excreta; in the case of Lassa fever, human-to-human transmission is possible.

Reservoirs for the Marburg and Ebola viruses are unknown, and human-to-human transmission occurs readily.

Many infections are asymptomatic. When symptomatic, they generally begin with a minor nonspecific flu-like illness that may evolve to one of a few syndromes (see Table 153-1). These syndromes include lymphadenopathy, rashes, aseptic meningitis, encephalitis, arthralgias, arthritis, and noncardiogenic pulmonary edema. Many cause fever and bleeding

[**Table 153-1.** Arbovirus, Arenavirus, and Filovirus Diseases]

tendencies (hemorrhagic fever). Decreased synthesis of vitamin K-dependent coagulation factors, disseminated intravascular coagulation, and altered platelet function contribute to bleeding.

Laboratory diagnosis often involves viral cultures, PCR, electron microscopy, and antigen and antibody detection where available.

Treatment

• Supportive care

• Sometimes ribavirin

Treatment for most of these infections is supportive. In hemorrhagic fevers, bleeding may require phytonadione (see p. 46 under Vitamin K Deficiency). Transfusion of packed RBCs or fresh frozen plasma may also be necessary. Aspirin and other NSAIDs are contraindicated because of antiplatelet activity.

Ribavirin 30 mg/kg IV (maximum, 2 g) loading dose followed by 16 mg/kg IV (maximum, 1 g/dose) q 6 h for 4 days, then 8 mg/kg IV (maximum, 500 mg/dose) q 8 h for 6 days is recommended for hemorrhagic fever caused by arenaviruses or bunyaviruses including Lassa fever, Rift Valley fever, and Crimean-Congo hemorrhagic fever. For dosage in hemorrhagic fever with renal syndrome, see p. . Antiviral treatment for other syndromes has not been adequately studied.

Prevention

Diseases transmitted by mosquitoes or ticks can often be prevented by wearing clothing that covers as much of the body as possible, using insect repellants, and minimizing the likelihood of exposure to the insect (eg, for mosquitoes, limiting time outdoors in wet areas; for ticks, see).

Diseases transmitted by rodent excreta can be prevented by sealing sites of potential rodent entry into homes and nearby buildings, preventing rodent access to food, and eliminating potential nesting sites around the home. Guidelines for cleaning and working in areas with potential rodent excreta are available through the Centers for Disease Control and Prevention (CDC).

Dengue

(Breakbone Fever; Dandy Fever)

Dengue is a mosquito-borne disease caused by a flavivirus. Dengue fever usually results in abrupt onset of high fever, headache, myalgias, arthralgias, and lymphadenopathy, followed by a rash that appears with a 2nd temperature rise after an afebrile period. Respiratory symptoms, such as cough, sore throat, and rhinorrhea, can occur. Dengue can also cause potentially fatal hemorrhagic fever with bleeding tendency and shock. Diagnosis involves serologic testing and PCR. Treatment is symptomatic and, for dengue hemorrhagic fever, includes meticulously adjusted intravascular volume replacement.

Dengue is endemic to the tropical regions of the world in latitudes from about 35° north to 35° south. Outbreaks are most prevalent in Southeast Asia but also occur in the Caribbean, including Puerto Rico and the US Virgin Islands, Oceania, and the Indian subcontinent; more recently, dengue incidence has increased in Central and South America. Each year, only about 100 to 200 cases are imported to the US by returning tourists, but an estimated 50 to 100 million cases occur worldwide, with about 20,000 deaths.

The causative agent, a flavivirus with 4 serogroups, is transmitted by the bite of *Aedes* mosquitoes. The virus circulates in the blood of infected humans for 2 to 7 days; *Aedes* mosquitoes may acquire the virus when they feed on humans during this period.

Symptoms and Signs

After an incubation period of 3 to 15 days, fever, chills, headache, retro-orbital pain with eye movement, lumbar backache, and severe prostration begin abruptly. Extreme aching in the legs and joints occurs during the first hours, accounting for the traditional name of breakbone fever. The temperature rises rapidly to up to 40° C, with relative bradycardia. Bulbar and palpebral conjunctival injection and a transient flushing or pale pink macular rash (particularly of the face) may occur. Cervical, epitrochlear, and inguinal lymph nodes are often enlarged.

Fever and other symptoms persist 48 to 96 h, followed by rapid defervescence with profuse sweating. Patients then feel well for about 24 h, after which fever may occur again (saddle-back pattern), typically with a lower peak temperature than the first. Simultaneously, a blanching maculopapular rash spreads from the trunk to the extremities and face.

Mild cases of dengue, usually lacking lymphadenopathy, remit in < 72 h. In more severe disease, asthenia may last several weeks. Death is rare. Immunity to the infecting strain is long-lasting, whereas broader immunity to other strains lasts only 2 to 12 mo.

Diagnosis

• Acute and convalescent serologic testing

Dengue fever is suspected in patients in endemic areas if they develop sudden fever, headache, myalgias, and adenopathy, particularly with the characteristic rash or recurrent fever. Evaluation should rule out alternative diagnoses, especially malaria and leptospirosis. Diagnostic studies include serologic testing, antigen detection, and PCR of blood. Serologic testing involves hemagglutination inhibiting or complement fixation tests using paired sera, but cross-reactions with other flavivirus antibodies are possible. Antigen detection is available in some parts of the world (not in the US), and PCR is usually done only in laboratories with special expertise. Although rarely done and difficult, cultures can be done using mosquitoes or specialized cell lines in specialized laboratories.

CBC may show leukopenia by the 2nd day of fever; by the 4th or 5th day, the WBC count may be 2000 to 4000/μL with only 20 to 40% granulocytes. Urinalysis may show moderate albuminuria and a few casts.

Treatment

• Supportive care

Treatment is symptomatic. Acetaminophen can be used, but NSAIDs, including aspirin, should be avoided because bleeding is a risk. Aspirin increases the risk of Reye's syndrome in children and should be avoided for that reason.

Prevention

People in endemic areas should try to prevent mosquito bites. To prevent further transmission by mosquitoes, patients with dengue should be kept under mosquito netting until the 2nd bout of fever has resolved. Vaccines are being evaluated.

Dengue Hemorrhagic Fever

(Philippine, Thai, or Southeast Asian Hemorrhagic Fever; Dengue Shock Syndrome)

Dengue hemorrhagic fever (DHF) is a variant presentation that occurs primarily in children < 10 yr living in areas where dengue is endemic. DHF requires prior infection with the dengue virus. It is an immunopathologic disease; dengue virus-antibody immune complexes trigger release of vasoactive mediators by macrophages. The mediators increase vascular permeability, causing vascular leakage, hemorrhagic manifestations, hemoconcentration, and serous effusions, which lead to circulatory collapse (ie, dengue shock syndrome).

Symptoms and Signs

In adults, DHF begins with abrupt fever and headache and is initially indistinguishable from classic dengue. Shock and increasing illness may develop rapidly 2 to 6 days after onset. Bleeding tendencies occur, usually as purpura, petechiae, or ecchymoses at injection sites; sometimes as hematemesis, melena, or epistaxis; and occasionally as subarachnoid hemorrhage. Hepatomegaly is common, as is bronchopneumonia with or without bilateral pleural effusions. Myocarditis can occur. Mortality is usually < 1% in experienced centers but otherwise can range up to 30%.

Diagnosis

• Clinical and laboratory criteria

DHF is suspected in children with WHO-defined clinical criteria for the diagnosis: sudden fever that stays high for 2 to 7 days, hemorrhagic manifestations, and hepatomegaly. Hemorrhagic manifestations include at least a positive tourniquet test and petechiae, purpura, ecchymoses, bleeding gums, hematemesis, or melena. The tourniquet test is done by inflating a BP cuff to midway between the systolic and diastolic BP for 15 min. The number of petechiae that form within a 2.5-cm diameter circle are counted; > 20

petechiae suggests capillary fragility.

CBC, coagulation tests, urinalysis, liver function tests, and dengue serologic tests should be done. Thrombocytopenia (≤ l00,000 platelets/μL) and a prolonged PT characterize the coagulation abnormalities. There may be mild proteinuria and increases in AST levels. Complement fixation antibody titers against flaviviruses are usually high.

Patients with WHO-defined clinical criteria plus thrombocytopenia (≤ 100,000/μL) or hemoconcentration (Hct increased by ≥ 20%) are presumed to have the disease.

Treatment

• Supportive care

Patients require intensive treatment to maintain euvolemia. Both hypovolemia (which can cause shock) and overhydration (which can cause acute respiratory distress syndrome) should be avoided. Urine output and the degree of hemoconcentration can be used to monitor intravascular volume.

No antivirals have been shown to improve outcome.

Hantavirus Infection

Bunyaviridae contain the genus Hantavirus, which consists of at least 4 serogroups with 9 viruses causing 2 major, sometimes overlapping, clinical syndromes:

• Hemorrhagic fever with renal syndrome (HFRS)

• Hantavirus pulmonary syndrome (HPS)

Viruses causing HFRS are Hantaan, Seoul, Dobrava (Belgrade), and Puumala. Those causing HPS are Sin Nombre, Black Creek Canal, Bayou, and New York-1.

Hantaviruses occur throughout the world in wild rodents, which shed the virus throughout life in urine and feces. Transmission occurs between rodents. Transmission to humans is through inhalation of aerosols of rodent excreta. Recent evidence suggests human-to-human transmission may occur rarely. Naturally and laboratory-acquired infections are becoming more common.

Laboratory diagnosis of Hantavirus infection is established by serologic tests and reverse transcriptase-PCR (RT-PCR). Serologic tests include enzyme-linked immunosorbent assay (ELISA) and Western and strip immunoblot assays. Growth of the virus is technically difficult and requires a biosafety level 3 laboratory.

Hemorrhagic Fever With Renal Syndrome

(Epidemic Nephrosonephritis; Korean Hemorrhagic Fever; Nephropathia Epidemica)

Hemorrhagic fever with renal syndrome (HFRS) begins as a flu-like illness and may progress to shock, bleeding, and renal failure. Diagnosis is with serologic tests and PCR. Mortality is 6 to 15%. Treatment includes IV ribavirin.

Some forms of HFRS are mild (eg, nephropathia epidemica, caused by Puumala virus, as occur in Scandinavia, the western part of the former Soviet Union, and Europe). Others are severe (eg, those caused by Hantaan, Seoul, and Dobrava viruses, as occur in Korea or the Balkans).

Symptoms and Signs

Incubation is about 2 wk. In mild forms, infection is often asymptomatic. When symptoms occur, onset is sudden, with high fever, headache, backache, and abdominal pain. On the 3rd or 4th day, subconjunctival

hemorrhages, palatal petechiae, and a truncal petechial rash may appear. Diffuse reddening of the face that resembles sunburn, with dermatographism, occurs in > 90% of patients. Relative bradycardia is present, and transient mild hypotension occurs in about half of patients, with shock in a minority. After the 4th day, renal failure develops. About 20% of patients become mentally obtunded. Seizures or severe focal neurologic symptoms occur in 1%. The rash subsides; patients develop polyuria and recover over several weeks. Proteinuria, hematuria, and pyuria may develop.

Diagnosis

• Serologic testing or PCR

HFRS is suspected in patients with possible exposure if they have fever, a bleeding tendency, and renal failure. CBC, electrolyte levels, renal function tests, coagulation tests, and urinalysis are then done. During the hypotensive phase, Hct increases and leukocytosis and thrombocytopenia develop. Albuminuria, hematuria, and RBC and WBC casts may develop, usually between the 2nd and 5th day. During the diuretic phase, electrolyte abnormalities are common.

Diagnosis of HFRS is ultimately based on serologic testing or PCR.

Prognosis

Death can occur during the diuretic phase, secondary to volume depletion, electrolyte disturbances, or secondary infections. Recovery usually takes 3 to 6 wk but may take up to 6 mo. Overall, mortality is 6 to 15%, almost always occurring in patients with the more severe forms. Residual renal dysfunction is uncommon except in the severe form that occurs in the Balkans.

Treatment

• Ribavirin

• Sometimes renal dialysis

Treatment is with IV ribavirin: loading dose 33 mg/kg (maximum, 2.64 g), followed by 16 mg/kg q 6 h (maximum, 1.28 g q 6 h) for 4 days, then 8 mg/kg q 8 h (maximum, 0.64 g q 8 h) for 3 days. Supportive care, which may include renal dialysis, is critical, particularly during the diuretic phase.

Hantavirus Pulmonary Syndrome

Hantavirus pulmonary syndrome (HPS) occurs in the US primarily in the southwestern states. It begins as a flu-like illness and, within days, causes noncardiogenic pulmonary edema. Diagnosis is with serologic tests and reverse transcriptase-PCR. Mortality is 50 to 75%. Treatment is supportive.

Most cases of HPS are caused by the Sin Nombre hantavirus (Four Corners virus, Muerto Canyon virus); others are caused by the Black Creek Canal virus or Bayou virus in the southeastern US, the New York virus on the East Coast of the US, or the Andes virus or Laguna Negra virus in South America. Infection is transmitted to humans via inhalation of excreta of sigmodontine rodents (especially the deer mouse). Most cases occur west of the Mississippi River in spring or summer, typically after heavy rains.

Symptoms and Signs

HPS begins as a nonspecific flu-like illness, with acute fever, myalgia, headache, and GI symptoms. Two to 15 days later (median 4 days), patients rapidly develop noncardiogenic pulmonary edema and hypotension. Several patients have had a combination of HFRS and HPS. Mild cases of HPS can occur.

Diagnosis

• Serologic testing or PCR

HPS is suspected in patients with possible exposure if they have unexplained clinical or radiographic pulmonary edema. Chest x-ray may show increased vascular markings, Kerley B lines, bilateral infiltrates, or pleural effusions. If HPS is suspected, echocardiography should be done to exclude cardiogenic pulmonary edema. CBC, liver function tests, and urinalysis are also usually done. HPS causes mild neutrophilic leukocytosis, hemoconcentration, and thrombocytopenia. Modest elevation of LDH, AST, and ALT, with decreased serum albumin, is typical. Urinalysis shows minimal abnormalities.

Diagnosis is with serologic testing or reverse transcriptase-PCR.

Prognosis

Patients who survive the first few days improve rapidly and recover completely over 2 to 3 wk, often without sequelae. Mortality is 50 to 75%.

Treatment

• Supportive care

Treatment is supportive. Mechanical ventilation, meticulous volume control, and vasopressors may be required. For severe cardiopulmonary insufficiency, extracorporal mechanical oxygenation may be lifesaving. IV ribavirin is ineffective.

Lassa Fever

Lassa fever is an often fatal arenavirus infection that occurs mostly in Africa. It may involve multiple organ systems but spares the CNS. Diagnosis is with serologic tests and PCR. Treatment includes IV ribavirin.

Lassa fever outbreaks have occurred in Nigeria, Liberia, and Sierra Leone. Cases have been imported to the US and the United Kingdom. The reservoir is *Mastomys natalensis*, a rat that commonly inhabits houses in Africa. Most human cases probably result from contamination of food with rodent urine, but human-to-human transmission can occur via urine, feces, saliva, vomitus, or blood.

Symptoms and Signs

The incubation period is 5 to 16 days. Symptoms begin with gradually progressive fever, weakness, malaise, and GI symptoms (eg, nausea, vomiting, diarrhea, dysphagia, stomach ache); symptoms and signs of hepatitis may occur. Over the subsequent 4 to 5 days, symptoms progress to prostration with sore throat, cough, chest pain, and vomiting. The sore throat becomes more severe during the first week; patches of white or yellow exudate may appear on the tonsils, often coalescing into a pseudomembrane.

In 60 to 80% of patients, systolic BP is < 90 mm Hg with pulse pressures of < 20 mm Hg, and relative bradycardia is possible. Facial and neck swelling and conjunctival edema occur in 10 to 30%. Occasionally, patients have tinnitus, epistaxis, bleeding from the gums and venipuncture sites, maculopapular rash, cough, and dizziness. Sensorineural hearing loss develops in 20%; it is often permanent.

In patients who will recover, defervescence occurs; fatally ill patients often develop shock, delirium, rales, pleural effusion, and, occasionally, generalized seizures. Pericarditis occasionally occurs. Degree of fever and aminotransferase levels correlate with disease severity. Late sequelae include alopecia, iridocyclitis, and transient blindness.

Diagnosis

• PCR or serologic testing

Lassa fever is suspected in patients with possible exposure if they have a viral prodrome followed by

unexplained disease of any organ system except the CNS. Liver function tests, urinalysis, serologic tests, and possibly CBC should then be done. Proteinuria is common and may be massive. AST and ALT levels rise (to 10 times normal), as do LDH levels. The most rapid diagnostic test is PCR, but demonstrating either Lassa IgM antibodies or a 4-fold rise in IgG antibody titer using an indirect fluorescent antibody technique is also diagnostic. Although the virus can be grown in cell culture, cultures are not routine. Because infection is a risk, particularly in patients with hemorrhagic fever, cultures must be handled only in a biosafety level 4 laboratory. Chest x-rays, obtained if lung involvement is suspected, may show basilar pneumonitis and pleural effusions.

Prognosis

Recovery or death usually occurs 7 to 31 days (average 12 to 15 days) after symptoms begin. Mortality is 16 to 45%. Disease is severe during pregnancy. Mortality is 50 to 92% in women who are pregnant or who have delivered within 1 mo. Most pregnant women lose the fetus.

Treatment

• Ribavirin

Ribavirin, if begun within the first 6 days, may reduce mortality up to 10-fold. Treatment with ribavirin is 30 mg/kg IV (maximum, 2 g) loading dose followed by 16 mg/kg IV (maximum, 1 g/dose) q 6 h for 4 days, then 8 mg/kg IV (maximum, 500 mg/dose) q 8 h for 6 days. Anti-Lassa fever plasma may be used as adjunctive therapy in very ill patients. Supportive treatment, including correction of fluid and electrolyte imbalances, is imperative. For infected pregnant women, particularly during the 3rd trimester, uterine evacuation appears to reduce maternal mortality.

Prevention

Universal precautions, airborne isolation (including use of goggles, high-efficiency masks, a negative-pressure room, and positive-pressure filtered air respirators), and surveillance of contacts are recommended.

Lymphocytic Choriomeningitis

Lymphocytic choriomeningitis is caused by an arenavirus. It usually causes a flu-like illness or aseptic meningitis, sometimes with rash, arthritis, orchitis, parotitis, or encephalitis. Diagnosis is by viral isolation or indirect immunofluorescence. Treatment is supportive.

Lymphocytic choriomeningitis is endemic in rodents. Human infection results most commonly from exposure to dust or food contaminated by the gray house mouse or hamsters, which harbor the virus and excrete it in urine, feces, semen, and nasal secretions. When transmitted by mice, the disease occurs primarily in adults during autumn and winter.

Symptoms and Signs

The incubation period is 1 to 2 wk. Most patients have no or minimal symptoms. Some develop a flu-like illness. Fever, usually 38.5 to 40° C, with rigors is accompanied by malaise, weakness, myalgia (especially lumbar), retro-orbital headache, photophobia, anorexia, nausea, and light-headedness. Sore throat and dysesthesia occur less often. After 5 days to 3 wk, patients may improve for 1 or 2 days. Many relapse with recurrent fever, headache, rashes, swelling of metacarpophalangeal and proximal interphalangeal joints, meningeal signs, orchitis, parotitis, or alopecia of the scalp.

Aseptic meningitis occurs in a minority of patients. Rarely, frank encephalitis, ascending paralysis, bulbar paralysis, transverse myelitis, or acute Parkinson's disease can occur. Neurologic sequelae are rare in meningitis but occur in up to 33% of patients with encephalitis. Infection may cause fetal abnormalities, including hydrocephalus and chorioretinitis.

Diagnosis

• CSF analysis, antibody detection, and viral culture

Lymphocytic choriomeningitis is suspected in patients with murine exposure and an acute illness, particularly aseptic meningitis or encephalitis. Aseptic meningitis may lower CSF glucose mildly but occasionally to as low as 15 mg/dL. CSF WBCs range from a few hundred to a few thousand cells, usually with > 80% lymphocytes. WBC counts of 2000 to 3000/μL and platelet counts of 50,000 to 100,000/μL typically occur during the first week of illness. Diagnosis can be made by isolating the virus from the blood or CSF or by indirect immunofluorescence assays of inoculated cell cultures, although these tests are most likely to be found in research laboratories. Diagnosis can also be made by detecting seroconversion of antibody to the virus.

Treatment

Treatment is supportive.

Marburg and Ebola Virus Infections

Marburg and Ebola are filoviruses that cause hemorrhage, multiple organ failure, and high mortality rates. Diagnosis is with enzyme-linked immunosorbent assay, PCR, or electron microscopy. Treatment is supportive. Strict isolation and quarantine measures are necessary to contain outbreaks.

Epidemics have occurred rarely and sporadically. Most index cases involve exposure to nonhuman primates from sub-Saharan Africa or the Philippines. The vector and reservoir are unknown, although the Marburg virus has been identified in bats, and cases have occurred in people exposed to bats.

Human-to-human transmission occurs via skin and mucous membrane contact with an infected person or other primate. Aerosol transmission has been postulated.

Symptoms and Signs

After an incubation period of 5 to 10 days, fever, myalgia, and headache occur, often with abdominal symptoms (nausea, vomiting, pain, diarrhea) and upper respiratory symptoms (cough, chest pain, pharyngitis). Photophobia, conjunctival injection, jaundice, and lymphadenopathy also occur. Delirium, stupor, and coma may occur, indicating CNS involvement. Hemorrhagic symptoms begin within the first few days and include petechiae, ecchymoses, and frank bleeding around puncture sites and mucous membranes. A maculopapular rash, primarily on the trunk, begins around day 5.

During the 2nd wk of symptoms, either defervescence occurs and patients begin recovery, or patients develop fatal multiple organ failure. Recovery is prolonged and may be complicated by recurrent hepatitis, uveitis, transverse myelitis, and orchitis. Mortality ranges from 25 to 90% (higher with Ebola).

Diagnosis

• Enzyme-linked immunosorbent blood assay and PCR

• Electron microscopy

Marburg or Ebola virus infection is suspected in patients with bleeding tendencies, fever, and travel to endemic areas or exposure to primates from these areas. CBC, routine blood chemistries, liver function and coagulation tests, and urinalysis are then done. Diagnostic tests include the enzyme-linked immunosorbent blood assay (ELISA) and PCR. The gold standard is detection of characteristic virions with electron microscopy of infected tissue (especially liver) or blood.

Treatment

• Supportive care

No effective antiviral therapy exists. Treatment is supportive and includes minimizing invasive procedures and replacing depleted coagulation factors.

Prevention

A vaccine is currently in development. Mask-gown-glove precautions, thorough equipment sterilization, hospital closures, and community education have shortened epidemics. All suspected cases, including the cadavers, require strict isolation and special handling.

The US has strict quarantine procedures to prevent importation of infected monkeys.

Case reporting is required.

Yellow Fever

Yellow fever is a mosquito-borne flavivirus infection endemic in tropical South America and sub-Saharan Africa. Symptoms may include sudden onset of fever, relative bradycardia, headache, and, if severe, jaundice, hemorrhage, and multiple organ failure. Diagnosis is with viral culture and serologic tests. Treatment is supportive. Prevention involves vaccination and mosquito control.

In urban yellow fever, virus is transmitted by the bite of an *Aedes aegypti* mosquito infected about 2 wk previously by feeding on a person with viremia. In jungle (sylvatic) yellow fever, the virus is transmitted by *Haemagogus* and other forest canopy mosquitoes that acquire the virus from wild primates. Incidence is highest during months of peak rainfall, humidity, and temperature in South America and during the late rainy and early dry seasons in Africa.

Symptoms and Signs

Infection ranges from asymptomatic (in 5 to 50% of cases) to a hemorrhagic fever with 50% mortality. Incubation lasts 3 to 6 days. Onset is sudden, with fever of 39 to 40° C, chills, headache, dizziness, and myalgias. The pulse is usually rapid initially but, by the 2nd day, becomes slow for the degree of fever (Faget's sign). The face is flushed, and the eyes are injected. Nausea, vomiting, constipation, severe prostration, restlessness, and irritability are common. Mild disease may resolve after 1 to 3 days. However, in moderate or severe cases, the fever falls suddenly 2 to 5 days after onset, and a remission of several hours or days ensues. The fever recurs, but the pulse remains slow. Jaundice, extreme albuminuria, and epigastric tenderness with hematemesis often occur together after 5 days of illness. There may be oliguria, petechiae, mucosal hemorrhages, confusion, and apathy.

Disease may last > 1 wk with rapid recovery and no sequelae. In the most severe form (called malignant yellow fever), delirium, intractable hiccups, seizures, coma, and multiple organ failure may occur terminally. During recovery, bacterial superinfections, particularly pneumonia, can occur.

Diagnosis

• Viral culture or serologic testing

Yellow fever is suspected in patients in endemic areas if they develop sudden fever with relative bradycardia and jaundice; mild disease often escapes diagnosis. CBC, urinalysis, liver function tests, coagulation tests, viral blood culture, and serologic tests should be done. Leukopenia with relative neutropenia is common, as are thrombocytopenia, prolonged clotting, and increased PT. Bilirubin and aminotransferase levels may be elevated acutely and for several months. Albuminuria, which occurs in 90% of patients, may reach 20 g/L; it helps differentiate yellow fever from hepatitis. In malignant yellow fever, hypoglycemia and hyperkalemia may occur terminally.

Diagnosis is confirmed by culture, serologic tests, PCR, or identification of characteristic midzonal hepatocyte necrosis at autopsy. Suspected or confirmed cases must be quarantined. Needle biopsy of

the liver during illness is contraindicated because hemorrhage is a risk.

Treatment

• Supportive care

Up to 10% of patients with disease severe enough to be diagnosed die.

Treatment is mainly supportive. Bleeding may be treated with vitamin K. An H_2 blocker and sucralfate can be helpful as prophylaxis for GI bleeding and can be used in all patients ill enough to require hospitalization.

Prevention

Preventive measures include

• Mosquito avoidance

• Vaccination

The most effective way to prevent outbreaks is to reduce the number of mosquitoes and limit mosquito bites by using diethyltoluamide (DEET), mosquito netting, and protective attire. During jungle outbreaks, people should evacuate the area until they are immunized and mosquitoes are controlled.

For people traveling to endemic areas, active immunization with the 17D strain of live-attenuated yellow fever vaccine (0.5 mL sc q 10 yr) is indicated and is effective in 95%. In the US, the vaccine is given only at US Public Health Service-authorized Yellow Fever Vaccination Centers. The vaccine is contraindicated in pregnant women, in infants < 6 mo, and in people with compromised immunity. If infants aged 6 to 8 mo cannot avoid travel to an endemic area, parents should discuss vaccination with their physician since the vaccine is typically not offered until age 9 mo.

To prevent further mosquito transmission, infected patients should be isolated in rooms that are well screened and sprayed with insecticides.

Other Infections

Chikungunya disease: This disease is an acute febrile illness followed by more chronic polyarthritis. It is transmitted by *Aedes* mosquitoes and is common in Africa, India, Guam, Southeast Asia, New Guinea, and limited areas of Europe. Prevention involves avoiding mosquito bites.

Mayaro disease: This dengue-like disease is transmitted by mosquitoes. It is common in Brazil, Bolivia, and Trinidad. Prevention involves avoiding mosquito bites.

Tick-borne encephalitis: Initially, a mild flu-like illness occurs, accompanied by leukocytopenia and thrombocytopenia, which clears up within a few days. About 30% of patients develop more severe symptoms (eg, meningitis, meningoencephalitis). A vaccine is available in Europe and Russia.

California encephalitis: This encephalitis and related infections are transmitted by mosquitoes and occur in the US Midwest and probably worldwide. This infection causes symptoms (eg, fever, somnolence, obtundation, focal neurologic findings, seizures) primarily in children. Temporal lobe involvement may mimic herpes encephalitis; 20% of patients develop behavioral problems or recurrent seizures. Mortality rate is < 1%. No treatment is available.

Omsk hemorrhagic fever and Kyasanur Forest disease: These infections are transmitted by ticks or by direct contact with an infected animal (eg, rodent, monkey). Omsk hemorrhagic fever occurs in the former Soviet Union, including Siberia; Kyasanur Forest disease occurs in India. They are acute febrile illnesses accompanied by bleeding diathesis, low BP, leukopenia, and thrombocytopenia; some patients develop encephalitis in the 3rd wk. Mortality rate is < 3% for Omsk hemorrhagic fever and 3 to 5% for

Kyasanur Forest disease. Prevention involves avoiding tick bites and infected animals.

Rift Valley fever: This infection is spread by mosquitoes and transmitted by direct or indirect contact with the blood or organs of infected animals (eg, during slaughtering, butchering, or veterinary procedures), inhalation of infected aerosols, or ingestion of raw milk from infected animals. Rift Valley fever occurs in South Africa, eastern Africa, and Egypt. Rarely, it progresses to ocular disorders, meningoencephalitis, or a hemorrhagic form (which has a 50% mortality rate). A vaccine for livestock is available, and a human vaccine is under investigation.

Chapter 154. Human Immunodeficiency Virus

Introduction

(See also p. 2847, the National Institutes of Health's AIDSInfo web site, and the recommendations of the HIV Medicine Association of the Infectious Diseases Society of America: Primary care guidelines for the management of persons infected with HIV.)

Human immunodeficiency virus (HIV) infection results from 1 of 2 similar retroviruses (HIV-1 and HIV-2) that destroy CD4+ lymphocytes and impair cell-mediated immunity, increasing risk of certain infections and cancers. Initial infection may cause nonspecific febrile illness. Risk of subsequent manifestations—related to immunodeficiency—is proportional to the level of CD4+ lymphocytes. Manifestations range from asymptomatic carriage to AIDS, which is defined by serious opportunistic infections or cancers or a CD4 count of < 200/μL. HIV infection can be diagnosed by antibody or antigen testing. Screening should be routinely offered to all adults and adolescents. Treatment aims to suppress HIV replication by using combinations of drugs that inhibit HIV enzymes.

Retroviruses are enveloped RNA viruses defined by their mechanism of replication via reverse transcription to produce DNA copies that integrate in the host cell genome. Several retroviruses, including human T-lymphotropic virus (see Sidebar 154-1), cause disorders in people.

AIDS is defined as HIV infection that leads to any of the disorders in clinical category B or C of HIV infection (see
Table 154-1) or a CD4+ T lymphocyte (helper cell—see p. 1082) count of < 200/μL. The disorders in categories B and C are

• Serious opportunistic infections

• Certain cancers, such as Kaposi's sarcoma and non-Hodgkin lymphoma, to which defective cell-mediated immunity predisposes

• Neurologic dysfunction

Sidebar 154-1 HTLV Infections

Infection with human T-lymphotropic virus (HTLV) 1 or 2 can cause T-cell leukemias and lymphomas, lymphadenopathy, hepatosplenomegaly, skin lesions, and immunocompromise. Some immunocompromised patients develop infections similar to those that occur in patients with AIDS. HTLV-1 can also cause myelopathy (see Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy on p. 1812).

Most cases are transmitted from mother to child by breastfeeding, but HTLV-1 can be transmitted sexually and through blood.

HIV-1 causes most HIV infections worldwide, but HIV-2 causes a substantial proportion of infections in parts of West Africa. In some areas of West Africa, both viruses are prevalent and may coinfect patients. HIV-2 appears less virulent than HIV-1.

HIV-1 originated in rural central Africa in the first half of the 20th century, when a closely related chimpanzee virus first infected humans. Epidemic global spread began in the late 1970s, and AIDS was recognized in 1981. More than 40 million people are infected worldwide. Of the 3 million annual deaths and 11,000 new daily infections, 95% occur in the developing world, one half are in women, and one seventh are in children < 15 yr.

Transmission

Transmission of HIV requires contact with body fluids—specifically blood, semen, vaginal secretions, breast milk, saliva, or exudates from wounds or skin and mucosal lesions—that contain free virions or infected cells. Transmission is more likely with higher levels of virions, as is typical during primary infection, even when people are asymptomatic. Transmission by saliva or droplets produced by coughing or sneezing, although conceivable, is extremely unlikely. HIV is not transmitted by casual nonsexual contact as may occur at work, school, or home.

Transmission is generally by

• Direct transfer of bodily fluids through sexual intercourse

• Sharing of blood-contaminated needles

• Childbirth

• Breastfeeding

• Medical procedures (eg, transfusions, exposure to contaminated instruments)

Sexual practices such as fellatio and cunnilingus appear to be relatively low risk but not absolutely safe (see Table 154-2). Risk does not increase significantly if semen or vaginal secretions are swallowed. However, open sores in the mouth may increase risk. The sexual practices with the highest risks are those that cause mucosal trauma, typically intercourse. Anal-receptive intercourse poses the highest risk. Mucous membrane inflammation facilitates HIV transmission; sexually transmitted diseases such as gonorrhea, chlamydia, trichomoniasis, especially those that cause ulceration (eg, chancroid, herpes, syphilis), increase risk. In heterosexuals, the estimated risk per coital act is about 1/1000; however, risk is increased in early and advanced stages of HIV infection when HIV concentrations in plasma and genital fluid are higher, in younger people, and in people with ulcerative genital diseases.

HIV can be transmitted from mother to off-spring transplacentally or perinatally; without treatment, risk of transmission is about 25 to 35%. HIV is also excreted in breast milk, and breastfeeding by HIV-infected mothers may transmit HIV to about 75% of infants who had previously escaped infection. Because many women of childbearing age are infected, incidence of AIDS in children has increased (see p. 2847).

Risk of transmission after skin penetration with a medical instrument contaminated with infected blood is on average about 1/300 without treatment. Immediate antiretroviral treatment probably reduces risk to 1/1500. Risk appears to be higher if the wound is deep or if blood is inoculated (eg, with a contaminated hollow-bore needle). Risk of transmission from infected health care practitioners who take appropriate precautions is unclear but appears minimal. In the 1980s, one dentist transmitted HIV to ≥ 6 of his patients by unknown means. However, extensive investigations of patients cared for by other HIV-infected physicians, including surgeons, have uncovered few other cases.

Although screening of blood donors has minimized risk of transmission via transfusion, a small risk still exists because antibody-based screening tests may miss early infections (see Prevention on p. 1454). Current risk of transmitting HIV via blood transfusion is probably between 1/500,000 and 1/1,000,000 per unit transfused.

[**Table 154-1.** Clinical Categories of HIV Infection*]

[**Table 154-2.** HIV Transmission Risk of Several Sexual Activities]

Epidemiology

HIV has spread in 2 epidemiologically distinct patterns:

• Male homosexual intercourse or contact with infected blood (eg, through sharing needles in IV drug

users; before effective screening of donors, through transfusions)

• Heterosexual intercourse (affecting men and women equally)

The first pattern usually predominates in developed countries; the second pattern predominates in Africa, South America, and southern Asia. In some countries (eg, Brazil, Thailand), both patterns are common. In areas where heterosexual transmission is dominant, HIV infection follows routes of trade, transportation, and economic migration to cities and spreads secondarily to rural areas. In Africa, particularly southern Africa, the HIV epidemic has killed tens of millions of young adults, creating millions of orphans. Factors that perpetuate spread include poverty, poor education, a deficient system of medical care, and lack of effective drugs.

Many opportunistic infections that complicate HIV are reactivations of latent infections. Thus, epidemiologic factors that determine the prevalence of latent infections also influence risk of specific opportunistic infections. In many developing countries, prevalence of toxoplasmosis and TB is high in the general population, and thus enormous increases in active TB have followed the HIV epidemic in these countries. Similarly in the US, incidence of coccidioidomycosis, common in the Southwest, and histoplasmosis, common in the Midwest, has increased because of HIV infection. In the US and Europe, human herpesvirus 8 infection, which causes Kaposi's sarcoma, is common among homosexual and bisexual men but uncommon among other HIV patients. Thus, in the US, > 90% of AIDS patients who develop Kaposi's sarcoma are homosexual or bisexual men.

Pathophysiology

HIV attaches to and penetrates host T cells via CD4+ molecules and chemokine receptors (see Fig. 154-1). After attachment, HIV RNA and enzymes are released into the host cell. Viral replication requires that reverse transcriptase (an RNA-dependent DNA polymerase) copy HIV RNA, producing proviral DNA; this copying mechanism is prone to errors, resulting in frequent mutations. These mutations facilitate the generation of HIV that can resist control by the host's immune system and by antiretroviral drugs. Proviral DNA enters the host cell's nucleus and is integrated into the host DNA in a process that involves HIV integrase. With each cell division, the integrated proviral DNA is duplicated along with the host DNA. Proviral HIV DNA is transcribed to viral RNA and translated to HIV proteins, including the envelope glycoproteins 40 and 120. The HIV proteins are assembled into HIV virions at the inner cell membrane and budded from the cell surface;

[**Fig. 154-1.** Simplified HIV life cycle.]

each host cell may produce thousands of virions. After budding, protease, another HIV enzyme, cleaves viral proteins, converting the immature virion into a mature, infectious form.

Infected CD4+ lymphocytes produce > 98% of plasma HIV virions. A subset of infected CD4+ lymphocytes constitutes a reservoir of HIV that can reactivate (eg, if antiviral treatment is stopped).

Virions have a plasma half-life of about 6 h. In moderate to heavy HIV infection, about 10^8 to 10^9 virions are created and removed daily. The high volume of HIV replication and high frequency of transcription errors by HIV reverse transcriptase result in many mutations, increasing the chance of producing strains resistant to host immunity and drugs.

Immune system: The main consequence of HIV infection is damage to the immune system, specifically loss of CD4+ lymphocytes, which are involved in cell-mediated and, to a lesser extent, humoral immunity. CD4+ lymphocyte depletion may result from the following:

• Direct cytotoxic effects of HIV replication

• Cell-mediated immune cytotoxicity

• Thymic damage that impairs lymphocyte production

Infected CD4+ lymphocytes have a half-life of about 2 days, which is much shorter than that of uninfected

CD4+ cells. Rates of CD4+ lymphocyte destruction correlate with plasma HIV level. Typically, during the initial or primary infection, HIV levels are highest (> 10^6 copies/mL), and the CD4 count drops rapidly. The normal CD4 count is about 750/μL, and immunity is minimally affected if the count is > 350/μL. If the count drops below about 200/μL, a variety of opportunistic pathogens may produce clinical disease, often by reactivating from latent states.

The humoral immune system is also affected. Hyperplasia of B cells in lymph nodes occurs, causing lymphadenopathy, and secretion of antibodies to previously encountered antigens increases, often leading to hyperglobulinemia. Total antibody levels (especially IgG and IgA) and titers against previous antigens (eg, cytomegalovirus [CMV]) may be unusually high. However, response to new antigens (eg, in vaccines) decreases as the CD4 count decreases.

Other tissues: HIV also infects nonlymphoid monocytic cells (eg, dendritic cells in the skin, macrophages, brain microglia) and cells of the heart and kidneys, causing disease in the corresponding organ systems. HIV strains in several compartments, such as the nervous system (brain and CSF) and genital tract (semen), can be genetically distinct from those in plasma. Thus, HIV levels and resistance patterns in these compartments may differ from those in plasma.

Disease progression: Antibodies to HIV are measurable usually within a few weeks after primary infection; however, antibodies cannot fully control HIV infection because mutated forms of HIV that are not controlled by the patient's current antibodies are generated.

Risk and severity of opportunistic infections, AIDS, and AIDS-related cancers are determined by 2 factors:

• CD4 count

• Exposure to potentially opportunistic pathogens

Plasma HIV virion levels, expressed as HIV RNA copies/mL, stabilize after about 6 mo at values (set points) that vary widely among patients but average 30,000 to 100,000/mL (4.2 to 5 $\log_{10}$/mL). The higher the set point, the more quickly the CD4 count decreases to a level that seriously impairs immunity (< 200/μL) and results in the opportunistic infections and cancers that define AIDS. Risk of specific opportunistic infections increases below threshold CD4 counts of about 200/μL for some and 50/μL for others. For example, risk of *Pneumocystis jirovecii* pneumonia, toxoplasmic encephalitis, and cryptococcal meningitis rises when the CD4 count is < 200/μL; CMV and *Mycobacterium avium* complex (MAC) infections are a risk when the CD4 count is < 50/μL. For every 3-fold (0.5 $\log_{10}$) increase in plasma HIV RNA in untreated patients, risk of progression to AIDS or death over the next 2 to 3 yr increases about 50%.

Without treatment, risk of progression to AIDS is about 1 to 2%/yr in the first 2 to 3 yr of infection and about 5 to 6%/yr thereafter. Eventually, AIDS almost invariably develops.

Symptoms and Signs

Initially, primary HIV infection may be asymptomatic or cause transient nonspecific symptoms (acute retroviral syndrome). Acute retroviral syndrome usually begins within 1 to 4 wk of infection and usually lasts 3 to 14 days; it is characterized by fever, malaise, rash, arthralgia, generalized lymphadenopathy, and sometimes aseptic meningitis. Symptoms are often mistaken for infectious mononucleosis or benign, nonspecific viral syndromes.

After the first symptoms disappear, most patients, even without treatment, have no symptoms or only a few, mild, intermittent, nonspecific symptoms for a highly variable time period (2 to 15 yr).

Symptoms may result from HIV directly or from opportunistic infections. The following are most common:

• Lymphadenopathy

• White plaques due to oral candidiasis

• Painful rash due to herpes zoster

• Diarrhea

• Fatigue

• Fever with intermittent sweats

Asymptomatic, mild-to-moderate cytopenias (eg, leukopenia, anemia, thrombocytopenia) are also common. In some patients, progressive wasting occurs.

Eventually, when the CD4 count drops to < 200/μL, nonspecific symptoms may worsen and a succession of AIDS-defining illnesses (those in category B or C of Table 154-1) develop. Evaluation may detect infection by *Mycobacterium* sp, *P. jirovecii*, *Cryptococcus neoformans*, or other fungi. Infections that also occur in the general population but suggest AIDS if they are unusually severe or frequently recur include herpes zoster, herpes simplex, vaginal candidiasis, and *Salmonella* sepsis. In patients with HIV infection, certain syndromes are common and may require different considerations (see Table 154-3). Some patients present with cancers (eg, Kaposi's sarcoma, B-cell lymphomas) that occur more frequently, are unusually severe, or have unique features in patients with HIV infection (see p. 1457). In other patients, neurologic dysfunction may occur.

[**Table 154-3.** Common Manifestations of HIV Infection by Organ System]

Diagnosis

• HIV antibody testing

• Nucleic acid amplification assays to determine HIV RNA level (viral load)

HIV infection is suspected in patients with persistent, unexplained, generalized adenopathy or any of the disorders in category B or C (see Table 154-1). It may also be suspected in high-risk patients with symptoms that could represent acute primary HIV infection.

Detection of antibodies to HIV is sensitive and specific except during the first few weeks after infection. Enzyme-linked immunosorbent assay (ELISA) to detect HIV antibodies is highly sensitive, but rarely, results are false-positive. Positive ELISA results are therefore confirmed with a more specific test such as Western blot. However, these tests have drawbacks:

• ELISA requires complex equipment.

• Western blot requires well-trained technicians and is expensive.

• The full testing sequence takes time.

Newer point-of-care tests using blood or saliva (eg, particle agglutination, immunoconcentration, immunochromatography) can be done quickly and simply, allowing testing in a variety of settings and immediate reporting to patients. Positive results of these tests should be confirmed by standard blood tests (eg, Western blot).

If HIV infection is suspected despite negative antibody test results (eg, during the first few weeks), plasma may be tested for HIV RNA (virion). The nucleic acid amplification assays used are highly sensitive and specific. HIV RNA assays require advanced technology, such as reverse transcription-PCR (RT-PCR) or branched DNA (bDNA) measurement, which are sensitive to extremely low HIV RNA levels. Measurement of p24 HIV antigen by ELISA is a less sensitive and less specific alternative for directly detecting HIV protein in blood.

When HIV is diagnosed, CD4 count and plasma HIV RNA level should be determined; both are useful for determining prognosis and monitoring treatment. The CD4 count is calculated as the product of the following:

• WBC count

• Percentage of WBCs that are lymphocytes

• Percentage of lymphocytes that are CD4+

Normally, the CD4 count in adults is about 750 ± 250/μL. Plasma HIV RNA level (viral load) reflects HIV replication rates. The higher the set point (the relatively stable virus levels that occur after primary infection), the more quickly the CD4 count decreases and the greater the risk of opportunistic infection, even in patients without symptoms.

HIV infection can be staged in order of increasing severity as category A, B, or C (see Table 154-1). Staging is by clinical manifestations or the CD4 count (A: ≥ 500; B: 200 to 499; and C: < 200/μL). The clinical category is determined by the most severe manifestation patients have had, past or present. Patients are never restaged to a less severe category.

HIV-related conditions: Diagnosis of the various opportunistic infections, cancers, and other syndromes that occur in HIV-infected patients is discussed elsewhere in THE MANUAL. Many have aspects unique to HIV infection (see Table 154-1 and p. 1457).

Hematologic disorders (eg, cytopenias, lymphomas, cancers) are common and may be usefully evaluated with bone marrow aspiration and biopsy. This procedure can also help diagnose disseminated infections with MAC, *M. tuberculosis, Cryptococcus, Histoplasma*, human parvovirus B19, *P. jirovecii*, and *Leishmania*. Most patients have normocellular or hypercellular marrow despite peripheral cytopenia, reflecting peripheral destruction. Iron stores are usually normal or increased, reflecting anemia of chronic disease (an iron-reutilization defect). Mild to moderate plasmacytosis, lymphoid aggregates, increased numbers of histiocytes, and dysplastic changes in hematopoietic cells are common.

HIV-associated neurologic syndromes can be differentiated via lumbar puncture with CSF analysis and contrast-enhanced CT or MRI (see Table 154-3 and elsewhere in THE MANUAL).

Screening: Screening antibody tests should be offered routinely to adults and adolescents, particularly pregnant women, regardless of their perceived risk. For people at highest risk, especially sexually active people who have multiple partners and who do not practice safe sex, testing should be repeated every 6 to 12 mo. Such testing is confidential and available, often free of charge, in many public and private facilities throughout the world.

Prognosis

Risk of AIDS, death, or both is predicted by the CD4 count in the short term and by plasma HIV RNA level in the longer term. For every 3-fold ($0.5 \log_{10}$) increase in viral load, mortality over the next 2 to 3 yr increases about 50%. HIV-associated morbidity and mortality vary by the CD count, with the most deaths from HIV-related causes occurring at counts of < 50/μL. However, with effective treatment, the HIV RNA level decreases to undetectable levels, CD4 counts often increase dramatically, and risk of illness and death falls.

A subgroup of HIV-infected persons (termed long-term nonprogressors) remains asymptomatic with high CD4 counts and low HIV levels in the blood without antiretroviral treatment. They usually have vigorous cellular and humoral immune responses to their infecting HIV strain as measured by assays in vitro. The specificity of this effective response is shown by examples of superinfection with a second strain of HIV to which their immune response is not as effective, resulting in their conversion to a more typical pattern of progression. Thus, their unusually effective response to the first strain did not apply to the second strain. These cases provide a rationale for counseling HIV-infected people not to expose themselves to possible HIV superinfection through unsafe sex or needle sharing.

Treatment

• Combinations of antiretroviral drugs

• Sometimes prophylaxis for opportunistic infections

Because adequate antiretroviral therapy can cause significant long-term morbidity, it is not recommended for everyone. Current indications include a CD4 count of < 350/μL and an HIV RNA level of > 55,000 copies/mL. Use of potent combinations of antiretroviral drugs for HIV therapy (highly active antiretroviral therapy [HAART]) aims to reduce the plasma HIV RNA level and restore the CD4 count (immune restoration or reconstitution). The lower the pretreatment CD4 count and the higher the HIV RNA level, the less likely treatment is to succeed; however, marked improvement is likely even in patients with advanced immunosuppression. The increase in CD4 count indicates a corresponding decrease in risk of opportunistic infections, other complications, and death. With immune restoration, patients, even those with complications that have no specific treatment (eg, HIV-induced cognitive dysfunction) or that were previously considered untreatable (eg, progressive multifocal leukoencephalopathy), may improve. Outcomes are also improved for patients with cancers (eg, lymphoma, Kaposi's sarcoma) and opportunistic infections.

HAART aims to suppress viral replication to undetectable levels; this goal can usually be achieved if patients take their drugs > 95% of the time. However, maintaining this degree of adherence is difficult. Partial suppression (failure to lower plasma levels to undetectable levels) may select for single or multiple mutations in HIV that make viruses completely or partially resistant and make subsequent treatment more likely to fail.

Patients beginning HAART sometimes deteriorate clinically, despite increasing CD4 counts, because of an immune reaction to subclinical opportunistic infections or to residual microbial antigens after successful treatment of opportunistic infections. These sometimes serious reactions are termed immune reconstitution inflammatory syndromes (IRIS). IRIS can complicate many infections and even cancers (eg, Kaposi's sarcoma) but is usually self-limited or responds to treatment with brief regimens of corticosteroids. Determining whether clinical deterioration is caused by treatment failure, IRIS, or both requires assessment of the persistence of active infection with cultures and can be difficult.

The success of HAART is assessed by measuring plasma HIV RNA levels every 4 to 8 wk for the first 4 to 6 mo or until HIV levels are undetectable (ie, < 50 copies/mL) and every 3 to 6 mo thereafter. Increasing levels are the earliest evidence of treatment failure and may precede a decreasing CD4 count by months. Maintaining patients on failing drug regimens contributes to development of HIV mutants that are more drug-resistant; however, compared with wild-type HIV, these mutants appear to reduce the CD4 count less.

If treatment fails, drug susceptibility (resistance) assays can determine the susceptibility of the dominant HIV strain to all available drugs. Genotypic and phenotypic assays are available and can help clinicians select a new regimen that should contain at least 2 and preferably 3 drugs. The dominant HIV strain in the blood of patients who are taken off antiretroviral therapy may revert over months to years to the wild type (which is susceptible) because resistant mutants replicate more slowly. Thus, if patients have not been treated recently, the full extent of resistance may not be apparent through resistance testing, but when treatment resumes, strains with resistance mutations often reemerge.

Several classes of antiretrovirals are used in HAART (see Table 154-4). There are 5 classes of antiretrovirals; 3 of them inhibit reverse transcriptase by blocking its RNA-dependent and DNA-dependent DNA polymerase activity.

• **Nucleoside reverse transcriptase inhibitors (NRTIs)** are phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and terminate synthesis of DNA chains.

• **Nucleotide reverse transcriptase inhibitors (nRTIs)** competitively inhibit the HIV reverse

transcriptase enzyme, as do NRTIs, but do not require initial phosphorylation.

• **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** bind directly to the reverse transcriptase enzyme.

• **Protease inhibitors (PIs)** inhibit the viral protease enzyme that is crucial to maturation of immature HIV virions after they bud from host cells.

• **Entry inhibitors (EIs),** sometimes called fusion inhibitors, interfere with the binding of HIV to CD4+ receptors and chemokine

[**Table 154-4.** Antiretroviral Drugs]

co-receptors; this binding is required for HIV to enter cells. For example, CCR-5 inhibitors block the CCR-5 receptor.

• **Integrase inhibitors** prevent HIV DNA from being integrated into human DNA.

Combinations of 3 or 4 drugs from different classes are usually necessary to fully suppress replication of wild-type HIV. The specific drugs are chosen based on factors such as concomitant conditions (eg, hepatic dysfunction) and other drugs being taken (to avoid drug interactions). To maximize adherence, clinicians should choose an affordable, well-tolerated regimen that uses once/day (preferable) or bid dosing. Guidelines from expert panels for initiating, selecting, switching, and interrupting therapy and special issues in treating women and children change regularly and are updated at www.aidsinfo.nih.gov/guidelines. Interactions between antiretrovirals may synergistically increase efficacy. For example, a subtherapeutic dose of ritonavir (100 mg once/day) can be combined with another PI (eg, lopinavir, amprenavir, indinavir, atazanavir, tipranavir). Ritonavir inhibits the hepatic enzyme that metabolizes the other PI, increasing the other drug's levels and efficacy. Another example is lamivudine (3TC) plus zidovudine (ZDV). Use of either drug as monotherapy quickly results in resistance, but the mutation that produces resistance in response to 3TC increases the susceptibility of HIV to ZDV. Thus, used together, they are synergistic.

Conversely, interactions between antiretrovirals may decrease the efficacy of each drug. One drug may increase elimination of another drug (eg, by inducing hepatic cytochrome P-450 enzymes responsible for elimination). Another, poorly understood effect of some NRTI combinations (eg, ZDV plus stavudine [d4T]) results in decreased antiretroviral activity without increasing drug elimination.

Combining drugs often increases the risk that either drug will have an adverse effect. Possible mechanisms include the following:

• **Hepatic metabolism of PIs by cytochrome P-450:** The result is decreased metabolism (and increased levels) of other drugs.

• **Additive toxicities:** For example, combining NRTIs, such as d4T and didanosine (ddI), increases the chance of adverse metabolic effects and peripheral neuropathy.

Many drugs may interfere with antiretrovirals; thus, interactions should always be checked before any new drug is started. In addition to drug interactions, grapefruit juice and St. John's wort can decrease activity of some antiretroviral drugs and should be avoided.

Adverse effects: Antiretrovirals can have serious adverse effects (see Table 154-4). Some of these effects, notably anemia, pancreatitis, hepatitis, and glucose intolerance, can be detected by blood tests before they cause symptoms. Patients should be screened regularly, both clinically and with appropriate laboratory testing (CBC and blood tests for hyperglycemia, hyperlidemia, hepatic damage, and renal function), especially when new drugs are started or unexplained symptoms develop.

Metabolic effects consist of interrelated syndromes of fat redistribution, hyperlipidemia, and insulin resistance. Subcutaneous fat is commonly redistributed from the face and distal extremities to the trunk

and abdomen—a cosmetic effect that can stigmatize and distress patients. Treating the resulting deep facial grooves with injected collagen or polylactic acid can be beneficial. Hyperlipidemia and hyperglycemia due to insulin resistance may occur with lipodystrophy. Drugs from all classes appear to contribute to these metabolic effects. Some, such as ritonavir or d4T, do so commonly; others, such as atazanavir, appear to have minimal effects on lipid levels.

Mechanisms for metabolic effects appear to be multiple; one is mitochondrial toxicity. Risk of metabolic effects (highest with PIs) and mitochondrial toxicity (highest with NRTIs) varies by drug class and within drug classes (eg, among NRTIs, highest with d4T). Effects are dose-dependent and often begin in the first 1 to 2 yr of treatment. Nonalcoholic steatohepatitis and lactic acidosis are uncommon but can be lethal. Long-term effects and optimal management of metabolic effects are unclear. Lipid-lowering drugs (statins) and insulin-sensitizing drugs (glitazones) may help. (See also the recommendations of the HIV Medicine Association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group: Guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving antiretroviral therapy.)

Bone complications of HAART include asymptomatic osteopenia and osteoporosis, which are common. Uncommonly, osteonecrosis of large joints such as the hip and shoulder causes severe joint pain and dysfunction. Mechanisms of bone complications are poorly understood.

Interruption of HAART is usually safe if all drugs are stopped simultaneously. Interruption may be necessary if intervening illnesses require treatment or if drug toxicity is intolerable or needs to be evaluated. After interruption to determine which drug is responsible for toxicity, clinicians can safely restart most drugs as monotherapy for up to a few days. NOTE: The most important exception is abacavir; patients who had fever or rash during previous exposure to abacavir may develop severe, potentially fatal hypersensitivity reactions with reexposure.

End-of-life care: Although antiretroviral therapy has dramatically increased life expectancy for patients with AIDS, many patients still deteriorate and die. Death may result from the following:

• Inability to take HAART consistently, resulting in progressive immunosuppression

• Occurrence of untreatable opportunistic infections and cancers

• Liver failure due to hepatitis B or C

Death is rarely sudden; thus, patients usually have time to make plans. Nonetheless, patients should record their plans for health care early, with clear instructions for end-of-life care. Other legal documents, including powers of attorney (see p. 3472) and wills, should be in place. These documents are particularly important for homosexual patients because protection of assets and rights (including visitation and decision-making) for their partners may be problems.

As patients near the end of life, clinicians may need to prescribe drugs to relieve pain, anorexia, agitation, and other distressing symptoms. The profound weight loss in many people during the last stages of AIDS makes good skin care difficult. The comprehensive support provided by hospice programs helps many patients because hospice providers are unusually skilled at symptom management, and they support caregivers and patient autonomy.

Prevention

Vaccines against HIV have been difficult to develop because HIV surface proteins mutate easily, resulting in an enormous diversity of antigenic types. Nonetheless, research continues, and various candidates are under study. At the present time, there is no effective AIDS vaccine.

Prevention of transmission: Vaginal microbicides (including antiretroviral drugs) inserted before sexual contact have proved ineffective, and some appear to increase risk for women, perhaps by damaging natural barriers to HIV.

Effective measures include the following:

- **Public education:** Education is effective and appears to have decreased rates of infection in some countries, notably Thailand and Uganda. Because sexual contact accounts for most cases, teaching people to avoid unsafe sex practices is the most relevant measure (see Table 154-2).

- **Safe sex practices:** Unless both partners are known to be free of HIV and remain monogamous, safe sex practices are essential. Safe sex practices are also advised when both partners are HIV-positive; unprotected sex between HIV-infected people may expose a person to resistant or more virulent strains of HIV and to other viruses (eg, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, hepatitis B virus) that cause severe disease in AIDS patients. Condoms offer the best protection. Oil-based lubricants should not be used because they may dissolve latex, increasing the risk of condom failure.

- **Counseling for parenteral drug users:** Counseling about the risk of sharing needles is important but is probably more effective if combined with provision of sterile needles, treatment of drug dependence, and rehabilitation.

- **Confidential testing for HIV infection:** Testing should be offered routinely to adolescents and adults in virtually all health care settings. To facilitate routine testing, some states no longer require written consent or extensive pre-test counseling.

- **Counseling for pregnant women:** If pregnant women test positive for HIV, risk of maternal-fetal transmission should be explained (see p. 2847). Monotherapy with ZDV or nevirapine reduces risk by two thirds, and 2- or 3-drug combination therapy probably reduces it even more. Some drugs can be toxic to the fetus or mother and cannot be guaranteed to prevent transmission. If treatment is indicated, combination therapy tailored to the woman's history and stage of pregnancy should be used throughout pregnancy. Cesarean delivery can reduce risk of transmission. Some women choose to terminate their pregnancy for this or other reasons.

- **Screening of blood and organs:** Transmission by blood transfusion is still possible because antibody results may be false-negative during early infection. Currently, screening blood for antibody and p24 antigen is mandated in the US and probably further reduces risk of transmission. Risk is reduced further by asking people with risk factors for HIV infection, even those with recent negative HIV antibody test results, not to donate blood or organs for transplantation.

- **Antiretrovirals:** Giving antiretrovirals to HIV-infected people reduces risk of transmission, but how much risk is reduced is unclear.

- **Circumcision of men:** In several African countries, circumcision reduced incidence by about 50%; it is probably also effective elsewhere.

- **Universal precautions:** Medical and dental health care practitioners should wear gloves in situations that may involve contact with any patient's mucous membranes or body fluids and should be taught how to avoid needlestick accidents. Home caregivers of patients with HIV infection should wear gloves if their hands may be exposed to body fluids. Surfaces or instruments contaminated by blood or other body fluids should be cleaned and disinfected. Effective disinfectants include heat, peroxide, alcohols, phenolics, and hypochlorite (bleach). Isolation of HIV-infected patients is unnecessary unless indicated by an opportunistic infection (eg, TB). Guidelines to prevent transmission from infected practitioners to patients have not been established.

Postexposure prophylaxis (PEP): Potential consequences of exposure to HIV have prompted the development of policies and procedures, particularly preventive treatment, to decrease risk of infection to health care workers. Preventive treatment is indicated after penetrating injuries involving HIV-infected blood (usually needlesticks) or heavy exposure of mucous membranes (eye or mouth) to infected fluids. Other body fluids of concern include

- Semen

• Vaginal secretions

• Body fluids obviously contaminated with blood

After initial exposure to blood, the exposed area is immediately cleaned with soap and water for skin exposures and with antiseptic for puncture wounds. If mucous membranes are exposed, the area is flushed with large amounts of water.

The following are documented:

• Nature and time of the exposure

• Clinical information, including risk factors and serologic tests for HIV, about the source patient for the exposure and the person exposed

Nature of the exposure is defined by

• Which body fluid was involved

• Whether exposure involved a penetrating injury (eg, needlestick, cut with sharp object)

• Whether the fluid had contact with nonintact skin (eg, abraded or chapped skin) or mucous membrane

Risk of infection is categorized as high or low:

• High: Involves a hollow-bore needle with visible blood, direct exposure to a needle from a vein or an artery of the source patient, or mucocutaneous exposure with a large amount of blood from a high-risk source (viral load > 1500 copies/mL)

• Low: Involves a solid needle, superficial injury, or a low-risk source (viral load < 1500 copies/mL) and includes most mucocutaneous exposures

Risk is about 0.3% after percutaneous exposure and about 0.09% after mucous membrane exposure.

The source is qualified by whether it is known or unknown; if the source is unknown (eg, a needle on the street or in a sharps disposal container), risk should be assessed based on the circumstances of the exposure (eg, whether the exposure occurred in an area where injection drug use is prevalent, whether a needle discarded in a drug-treatment facility was used). If the source is known but HIV status is not, the source is assessed for HIV risk factors, and prophylaxis is considered (see Table 154-5).

The goal is to start PEP as soon after exposure as possible if prophylaxis is warranted. CDC recommends providing PEP within 24 to 36 h after exposure; a longer interval after exposure requires the advice of an expert.

Use of PEP is determined by risk of infection; guidelines recommend antiretroviral therapy with 2 NRTIs (eg, ZDV plus 3TC) for low risk and the addition of one or more drugs (eg, 2 NRTIs plus a PI or an NNRTI) for high risk; drugs are given for 28 days. Nevirapine is avoided because of the rare possibility of severe hepatitis. Although evidence is not conclusive, ZDV alone probably reduces risk of transmission after needlestick injuries by about 80%. For detailed recommendations, see www.cdc.gov/mmwr/PDF/rr/rr5011.pdf or www.nccc.ucsf.edu/Hotlines/PEPline.html.

If the source's virus is known or suspected to be resistant to ≥ 1 drug, an expert in antiretroviral therapy and HIV transmission should be consulted. However, clinicians should not delay PEP pending expert consultation or drug susceptibility testing. Also, clinicians should provide immediate evaluation and face-to-face counseling and not delay follow-up care.

Prevention of opportunistic infections: Effective chemoprophylaxis is available for many opportunistic

infections and reduces rates of disease due to *P. jirovecii, Candida, Cryptococcus*, and MAC. If therapy restores CD4 counts to above threshold values for > 3 mo, chemoprophylaxis can be stopped.

Primary prophylaxis depends on CD count:

[**Table 154-5.** Postexposure Prophylaxis Recommendations]

• **CD4 count < 200/μL:** Prophylaxis against *P. jirovecii* pneumonia and toxoplasmic encephalitis is recommended. Double-strength trimethoprim/sulfamethoxazole (TMP/SMX) tablets given once/day or 3 times/wk are effective for both infections. Some adverse effects can be minimized with the 3 times/wk dose or by gradual dose escalation. Some patients who cannot tolerate TMP/SMX can tolerate dapsone (100 mg once/day). For the few patients who cannot tolerate either drug because of a troublesome adverse effect (eg, fever, neutropenia, rash), aerosolized pentamidine 300 mg once/day or atovaquone 1500 mg once/day can be used.

• **CD4 count < 75/μL:** Prophylaxis against disseminated MAC with azithromycin, clarithromycin, or rifabutin is recommended. Azithromycin can be given weekly as two 600-mg tablets; it provides protection (70%) similar to daily clarithromycin and does not interact with other drugs.

If latent TB is suspected (based on tuberculin skin tests, high-risk exposure, or prior history of infection), regardless of CD4 count, patients should be given either rifampicin 10 mg/kg po up to 600 mg or rifabutin 300 mg po daily plus either pyrazinamide 25 mg/kg po up to 2.5 g for 2 mo or isoniazid 5 mg/kg po up to 300 mg once/day for 9 mo to prevent reactivation.

For primary prophylaxis against some fungal infections (eg, esophageal candidiasis, cryptococcal meningitis or pneumonia), oral fluconazole 100 to 200 mg once/day or 400 mg weekly is successful but is infrequently used because the cost per infection prevented is high and diagnosis and treatment of these infections are usually successful.

Secondary prophylaxis is indicated if patients have had the following:

• Recurrent oral, vaginal, or esophageal candidiasis or cryptococcal infections: Fluconazole is used.

• Histoplasmosis: Itraconazole is used (see p. <u>1331</u>).

• Latent toxoplasmosis: This disorder is indicated by serum antibodies (IgG) to *Toxoplasma gondii*. TMP/SMX (in doses used to prevent *P. jirovecii* pneumonia) is used to prevent reactivation and consequent toxoplasmic encephalitis. Latent infection is less common (about 15% of adults) in the US than in Europe and most developing countries.

• *P. jirovecii* pneumonia (see p. <u>1935</u>)

• Herpes simplex infection (see p. <u>1417</u>)

• Aspergillosis (possibly—see p. <u>1323</u>)

Detailed guidelines for prophylaxis of fungal (including *Pneumocystis*), viral, mycobacterial, and toxoplasmic infections are available at www.aidsinfo.nih.gov/guidelines.

Vaccination: Vaccination (using nonviable vaccines) is indicated for pneumococcal disease (23-valent vaccine if the CD4 count is > 200/μL), influenza A (all patients annually), and hepatitis B and A (for patients at risk); these vaccines are effective less often in patients who are HIV-positive than in those who are HIV-negative. Vaccines against human papillomavirus and varicella (secondary boosting with varicella-zoster, consisting of high-titer live virus) would potentially be valuable in HIV-infected adults, and both are undergoing testing. But their safety needs to be evaluated because these live-virus vaccines are potentially dangerous for patients with severe immunosuppression. For children with HIV infection, vaccination recommendations vary (see p. <u>2857</u> and <u>Table 281-4</u> on p. <u>2859</u>).

Cancers Common in HIV-Infected Patients

Kaposi's sarcoma (see p.), non-Hodgkin lymphoma (see p.), and cervical cancer are AIDS-defining cancers in HIV-infected patients. Other cancers that appear to be increased in incidence or severity include Hodgkin lymphoma (especially the mixed cellularity and lymphocyte-depleted subtypes), primary CNS lymphoma, anal cancer, testicular cancer, melanoma and other skin cancers, and lung cancer. Leiomyosarcoma is a rare complication of HIV infection in children.

Non-Hodgkin lymphoma: Incidence is 50 to 200 times higher in HIV-infected patients. Most cases are B-cell, aggressive, high-grade histologic subtype lymphomas. At diagnosis, extranodal sites are usually involved; they include bone marrow, GI tract, and other sites that are unusual in non-HIV-associated non-Hodgkin lymphoma, such as the CNS and body cavities (eg, pleural, pericardial, peritoneal).

Common presentations include rapidly enlarging lymph nodes or extranodal masses or systemic symptoms (eg, weight loss, night sweats, fevers).

Diagnosis is by biopsy with histopathologic and immunochemical analysis of tumor cells. Abnormal circulating lymphocytes or unexpected cytopenias suggest involvement of the bone marrow, mandating bone marrow biopsy. Tumor staging may require CSF examination and CT or MRI of the chest, abdomen, and other areas where tumors are suspected.

Poor prognosis is predicted by the following:

• CD4 count of < 100/μL

• Age > 35 yr

• Poor functional status

• Bone marrow involvement

• History of opportunistic infections

• High-grade histologic subtype

Non-Hodgkin lymphoma is treated with systemic, multidrug chemotherapy (eg, cyclophosphamide, doxorubicin, and vincristine plus prednisone), usually combined with antiretrovirals, prophylactic antibiotics and antifungals, and hematologic growth factors. Therapy may be limited by severe myelosuppression, particularly when combinations of myelosuppressive antitumor or antiretroviral drugs are used. Another possible treatment is IV anti-CD20 monoclonal antibody (rituximab), which is effective for non-Hodgkin lymphoma in patients without HIV. Radiation therapy may debulk large tumors and control pain or bleeding.

Primary CNS lymphoma: Incidence is markedly increased in HIV-infected patients with very low CD4 counts (see also p.). These lymphomas consist of intermediate- or high-grade malignant B cells, originating in CNS tissue, and do not spread systemically.

Presenting symptoms include headache, seizures, neurologic deficits (eg, cranial nerve palsies), and mental status change.

Acute treatment requires control of cerebral edema and whole-brain radiation therapy. Radiographic response is common, but median survival is < 6 mo. The role of antitumor chemotherapy is unclear, but highly active antiretroviral therapy (HAART) improves survival.

Cervical cancer: In HIV-infected women, incidence of human papillomavirus (HPV) infection is increased, oncogenic subtypes (types 16, 18, 31, 33, 35, and 39) persist, and the incidence of cervical intraepithelial dysplasia (CIN) is up to 60%, but increased incidence of cervical cancer has not been

proved. However, cervical cancers, if they occur, are more extensive, are more difficult to cure, and have higher recurrence rates after treatment. Confirmed risk factors for cancer include the following:

• Infection with HPV subtype 16 or 18

• CD4+ count of < 200/μL

• Age > 34 yr

HIV infection does not change the management of CIN or cervical cancer. Frequent Papanicolaou tests are important to monitor for progression. HAART may result in resolution of HPV infection and regression of CIN but has no clear effects on cancer.

Squamous cell cancer of the anus and vulva: Squamous cell cancers of the anus (see also p. 195) and vulva (see also p. 2581) are caused by the same oncogenic types of HPV as cervical cancers and occur more commonly in HIV-infected patients. The reason for the increased incidence in these patients appears to be the increased rate of high-risk behaviors (eg, anal-receptive intercourse) rather than HIV itself. Anal dysplasia is common, and squamous cell cancers can be very aggressive.

Treatments include surgical extirpation, radiation therapy, and combined chemotherapy with mitomycin or cisplatin and 5-fluorouracil.

Chapter 155. Other Viruses

Introduction

The number of viral diseases affecting humans is large. Most of these are discussed elsewhere in THE MANUAL. A few are not easily categorized and are discussed here. Most of these diseases tend to occur in children but can occur in adults.

Measles

(Rubeola; Morbilli; 9-Day Measles)

Measles is a highly contagious, viral infection that is most common among children. It is characterized by fever, cough, coryza, conjunctivitis, enanthem (Koplik's spots) on the buccal or labial mucosa, and a maculopapular rash that spreads cephalocaudally. Diagnosis is usually clinical. Treatment is supportive. Vaccination is highly effective.

Worldwide, measles infects about 20 million people causing about 200,000 deaths annually, primarily in children. Measles is rare in the US because of routine childhood vaccination; an average of 63 cases/yr were reported to the Centers for Disease Control and Prevention (CDC) from 2000 to 2007. However, in 2008, 131 cases were reported from January to July.

Pathophysiology

Measles is caused by a paramyxovirus and is a human disease with no known animal reservoir or asymptomatic carrier state. It is extremely communicable; the secondary attack rate is > 90% among susceptible people who are exposed.

Measles is spread mainly by secretions from the nose, throat, and mouth during the prodromal or early eruptive stage. Communicability begins several days before and continues until several days after the rash appears. Measles is not communicable once the rash begins to desquamate.

Transmission is typically by large respiratory droplets that are discharged by cough and briefly remain airborne for a short distance. Transmission may also occur by small aerosolized droplets that can remain airborne (and thus can be inhaled) for up to 2 h in closed areas (eg, in an office examination room). Transmission by fomites seems less likely than airborne transmission because the measles virus is thought to survive only for a short time on dry surfaces.

An infant whose mother has had measles receives antibodies transplacentally; these antibodies are protective for most of the first 6 to 12 mo of life. Lifelong immunity is conferred by infection. In the US, many measles cases are imported by travelers or immigrants; indigenous transmission occurs primarily among unvaccinated people.

Symptoms and Signs

After a 7- to 14-day incubation period, measles begins with a prodrome of fever, coryza, hacking cough, and tarsal conjunctivitis. The pathognomonic Koplik's spots appear 2 to 4 days later, usually on the buccal mucosa opposite the 1st and 2nd upper molars. The spots resemble grains of white sand surrounded by red areolae. They may be extensive, producing diffuse mottled erythema of the buccal mucosa. Sore throat develops.

The rash (see
[Plate 65](#)) appears 3 to 5 days after symptom onset, usually 1 to 2 days after Koplik's spots appear. It begins on the face in front of and below the ears and on the side of the neck as irregular macules, soon mixed with papules. Within 24 to 48 h, lesions spread to the trunk and extremities (including the palms and soles) as they begin to fade on the face. Petechiae or ecchymoses may occur with severe rashes.

During peak disease severity, a patient's temperature may exceed 40°C, with periorbital edema,

conjunctivitis, photophobia, a hacking cough, extensive rash, prostration, and mild itching. Constitutional symptoms and signs parallel the severity of the eruption and the epidemic. In 3 to 5 days, the fever falls, the patient feels more comfortable, and the rash fades rapidly, leaving a coppery brown discoloration followed by desquamation.

Immunocompromised patients may not have a rash and can develop severe, progressive giant cell pneumonia.

Complications: Complications include

• Atypical measndrome

• Pneumonia

• Bacterial superinfection

• Acute thrombocytopenic purpura

• Encephalitis

• Transient hepatitis

• Subacute sclerosing panencephalitis

Atypical measles syndrome usually occurs in people previously immunized with the original killed-virus measles vaccines, which have been unavailable since 1968. The older vaccines can alter disease expression after infection with wild-type measles. Atypical measles syndrome may begin abruptly, with high fever, prostration, headache, abdominal pain, and cough. The rash may appear 1 to 2 days later, often beginning on the extremities, and may be maculopapular, vesicular, urticarial, or purpuric. Edema of the hands and feet may occur. Pneumonia and hilar adenopathy are common and may be prolonged; chest x-ray abnormalities may persist for weeks to months. Symptomatic hypoxemia may occur.

Pneumonia due to measles virus infection of the lungs occurs in about 5% of patients, even during apparently uncomplicated infection; in infants, it is a common cause of death.

Bacterial superinfections include pneumonia and otitis media. Measles transiently suppresses delayed hypersensitivity, which can worsen active TB and temporarily prevent reaction to tuberculin and histoplasmin antigens in skin tests. Bacterial superinfection is suggested by pertinent focal signs or a relapse of fever, leukocytosis, or prostration.

Acute thrombocytopenic purpura may occur after infection resolves and cause a mild, self-limited bleeding tendency, although occasionally bleeding is severe.

Encephalitis occurs in 1/1000 to 2000 cases, usually 2 days to 2 wk after onset of the rash, often beginning with recrudescence of high fever, headache, seizures, and coma. CSF usually has a lymphocyte count of 50 to 500/μL and a mildly elevated protein level but may be normal initially. Encephalitis may resolve in about 1 wk or may persist longer, causing morbidity or death.

Transient hepatitis may occur during an acute infection.

Subacute sclerosing panencephalitis (SSPE) is a rare, progressive, ultimately fatal, late complication of measles (see p.).

Diagnosis

• Clinical evaluation

• Serologic testing

• Viral detection via culture or reverse transcription-PCR

Typical measles may be suspected in an exposed patient who has coryza, conjunctivitis, photophobia, and cough but is usually suspected only after the rash appears. Diagnosis is usually clinical, by identifying Koplik's spots or the rash. CBC is unnecessary but, if obtained, may show leukopenia with a relative lymphocytosis. Laboratory identification is necessary for public health and outbreak control purposes. It is most easily done by demonstration of the presence of measles IgM antibody in an acute serum specimen or by viral culture or reverse transcription-PCR of throat swabs, blood, nasopharyngeal swabs, or urine samples. A rise in IgG antibody levels between acute and convalescent sera is highly accurate, but obtaining this information delays diagnosis. All cases of suspected measles should be reported to the local health department even before laboratory confirmation.

Differential diagnosis includes rubella, scarlet fever, drug rashes (eg, from phenobarbital or sulfonamides), serum sickness, roseola infantum, infectious mononucleosis, erythema infectiosum (see p. 2840), and echovirus and coxsackievirus infections (see also Table 149-7). Atypical measles, because of its greater variability, can simulate even more conditions than typical measles. Some of these conditions can be distinguished from typical measles as follows:

• **Rubella:** A recognizable prodrome is absent, fever and other constitutional symptoms are absent or less severe, postauricular and suboccipital lymph nodes are enlarged (and usually tender), and duration is short.

• **Drug rashes:** A drug rash often resembles the measles rash, but a prodrome is absent, there is no cephalocaudal progression or cough, and there is usually a history of recent drug exposure.

• **Roseola infantum:** The rash resembles that of measles, but it seldom occurs in children > 3 yr. Initial temperature is usually high, Koplik's spots and malaise are absent, and defer-vescence and rash occur simultaneously.

Prognosis

Mortality is about 2/1000 in the US but is much higher in the developing world. Undernutrition and vitamin A deficiency may predispose to mortality. Vitamin A supplementation is recommended for populations at risk.

Treatment

• Supportive care

• For children, vitamin A

Treatment is supportive, including for encephalitis.

Vitamin A supplementation has been shown to reduce morbidity and mortality due to measles in children in the developing world. Because low serum levels of vitamin A are associated with severe disease due to measles, vitamin A treatment is recommended for all children with measles. The dose is given orally once/day for 2 days and depends on the child's age:

• > 1 yr: 200,000 IU

• 6 to 11 mo: 100,000 IU

• < 6 mo: 50,000 IU

In children with clinical signs of vitamin A deficiency, a single age-specific dose of vitamin A is repeated 2 to 4 wk later.

Prevention

A live-attenuated virus vaccine containing measles, mumps, and rubella is routinely given to children in most developed countries (see also p. 1177 and
Table 268-10 on p. 2718). The first dose is recommended at age 12 to 15 mo but can be given as young as age 6 mo during a measles outbreak. Two doses are recommended; the second is given at age 4 to 6 yr. Infants immunized at < 1 yr of age still require 2 further doses given after the first birthday. Vaccine provides long-lasting immunity and has decreased measles incidence in the US by 99%. The vaccine causes mild or inapparent, noncommunicable infection. Fever > 38° C occurs 5 to 12 days after inoculation in < 5% of vaccinees and can be followed by a rash. CNS reactions are exceedingly rare; the vaccine does not cause autism.

Contraindications to the vaccine include generalized cancers (eg, leukemia, lymphoma), immunodeficiency, and therapy with immunosuppressants (eg, corticosteroids, irradiation, alkylating agents, antimetabolites). HIV infection is a contraindication only if immunosuppression is severe (CDC immunologic category 3 with CD4 < 15%); if not, the risks of wild measles outweigh the risk of acquiring measles from the live vaccine. Reasons to defer vaccination include pregnancy, serious febrile illness, active untreated TB, or administration of antibody (as whole blood, plasma, or any immune globulin). Duration of deferral depends on the type and dose of immune globulin preparation given but may be as long as 11 mo.

Postexposure prophylaxis: Prevention in susceptible contacts is possible by giving the vaccine within 3 days of exposure. If vaccine should be deferred, immune globulin 0.25 mL/kg IM (maximum dose, 15 mL) is given immediately, with vaccination given 5 to 6 mo later if medically appropriate (eg, if the patient is no longer pregnant). An exposed immunodeficient patient with a contraindication to vaccination is given immune globulin 0.5 mL/kg IM (maximum, 15 mL). Immune globulin should not be given simultaneously with vaccine.

Monkeypox

Monkeypox virus is structurally related to the smallpox virus and causes similar, but milder illness.

Monkeypox, like smallpox, is a member of the Orthopoxvirus group. Although the reservoir is unknown, monkeypox is endemic among rodents and monkeys in the rain forests of Africa, mostly in western and central Africa. Human disease occurs in Africa sporadically and in occasional epidemics.

In the US, an outbreak of monkeypox occurred in 2003, when infected rodents imported as pets from Ghana spread the virus to pet prairie dogs, which then infected people in the Midwest. The outbreak involved 35 confirmed, 13 probable, and 22 suspected cases in 6 states, but there were no deaths.

Monkeypox is probably transmitted from animals via wounds or mucous membranes. Person-to-person transmission occurs inefficiently, with an attack rate of 8 to 9%. Most patients are children. People who have received smallpox vaccine may be at reduced risk. In Africa, mortality rate ranges from 4 to 22%.

Clinically, monkeypox is similar to smallpox; however, skin lesions occur more often in crops, and lymphadenopathy may be more common.

Clinical differentiation of monkeypox from smallpox and chickenpox may be impossible. Diagnosis is by culture, PCR, immunohistochemistry, or electron microscopy, depending on which tests are available.

Treatment is supportive. Cases are reported to public health authorities.

Mumps

(Epidemic Parotitis)

Mumps is an acute, contagious, systemic viral disease, usually causing painful enlargement of

the salivary glands, most commonly the parotids. Complications may include orchitis, meningoencephalitis, and pancreatitis. Diagnosis is usually clinical; all cases are reported to public health authorities. Treatment is supportive. Vaccination is effective for prevention.

The causative agent, a paramyxovirus, is spread by droplets or saliva. The virus probably enters through the nose or mouth. It is in saliva up to 6 days before salivary gland swelling appears. It is also in blood and urine and, if the CNS is involved, in CSF. One attack usually confers permanent immunity.

Mumps is less communicable than measles. It occurs mainly in unimmunized populations, but outbreaks on college campuses among largely immunized populations have occurred. A combination of primary vaccine failure (failure to develop immunity after vaccination) and waning immunity may have played a part in these outbreaks. In 2006, there was a resurgence of mumps in the US with 6584 cases, which occurred primarily in young adults with prior vaccination. As with measles, mumps cases may be imported, leading to indigenous transmission, especially in congregate settings (eg, college campuses). Peak incidence of mumps is during late winter and early spring. Disease occurs at any age but is unusual in children < 2 yr, particularly those < 1 yr. About 25 to 30% of cases are clinically inapparent.

Symptoms and Signs

After a 14- to 24-day incubation period, most people develop headache, anorexia, malaise, and a low- to moderate-grade fever. The salivary glands become involved 12 to 24 h later, with fever up to 39.5 to 40° C. Fever persists 24 to 72 h. Glandular swelling peaks on about the 2nd day and lasts 5 to 7 days. Involved glands are extremely tender during the febrile period.

Parotitis is usually bilateral. Pain while chewing or swallowing, especially while swallowing acidic liquids such as vinegar or citrus juice, is its earliest symptom. It later causes swelling beyond the parotid in front of and below the ear. Occasionally, the submandibular and sublingual glands also swell and, more rarely, are the only glands affected. Submandibular gland involvement causes neck swelling beneath the jaw, and suprasternal edema may develop, perhaps because of lymphatic obstruction by enlarged salivary glands. When sublingual glands are involved, the tongue may swell. The oral duct openings of the affected glands are edematous and slightly inflamed. The skin over the glands may become tense and shiny.

Complications: Mumps may involve organs other than the salivary glands, particularly in postpubertal patients. Such complications include

• Orchitis or oophoritis

• Meningitis or encephalitis

• Pancreatitis

About 20% of postpubertal male patients develop orchitis (testicular inflammation), usually unilateral, with pain, tenderness, edema, erythema, and warmth of the scrotum. Some testicular atrophy may ensue, but testosterone production and fertility are usually preserved. In females, oophoritis (gonadal involvement) is less commonly recognized, is less painful, and does not impair fertility.

Meningitis, typically with headache, vomiting, stiff neck, and CSF pleocytosis, occurs in 1 to 10% of patients with parotitis. Encephalitis, with drowsiness, seizures, or coma, occurs in about 1/1000 to 5000 cases. About 50% of CNS mumps infections occur without parotitis.

Pancreatitis, typically with sudden severe nausea, vomiting, and epigastric pain, may occur toward the end of the first week. These symptoms disappear in about 1 wk, leading to complete recovery.

Prostatitis, nephritis, myocarditis, hepatitis, mastitis, polyarthritis, deafness, and lacrimal gland involvement occur extremely rarely. Inflammation of the thyroid and thymus glands may cause edema and swelling over the sternum, but sternal swelling more often results from submandibular gland involvement.

Diagnosis

• Clinical evaluation

• Serologic testing

• Viral detection via tissue culture or reverse transcription-PCR

Mumps is suspected in patients with salivary gland inflammation and typical systemic symptoms, particularly if there is parotitis or a known mumps outbreak. Laboratory testing is not needed to make a diagnosis but is strongly recommended for public health purposes. Other conditions can cause similar glandular involvement (see
Table 155-1). Mumps is also suspected in patients with unexplained aseptic

[**Table 155-1.** Causes of Parotid and Other Salivary Gland Enlargement]

meningitis or encephalitis during mumps outbreaks. Lumbar puncture is necessary for patients with meningeal signs.

Laboratory diagnosis is necessary if disease is unilateral, is recurrent, occurs in previously immunized patients, or causes prominent involvement of tissues other than the salivary glands. Testing is also recommended for all patients with parotitis lasting ≥ 2 days without an identified cause. Acute and convalescent sera are tested by complement fixation or enzyme-linked immunosorbent assays (ELISA). If the laboratory is capable, the virus can usually be cultured from the throat, CSF, and occasionally the urine, or viral RNA can be detected by reverse transcription-PCR.

Other laboratory tests are generally unnecessary, although serum amylase level can also be measured; elevation suggests mumps. WBC count is nonspecific; it may be normal but usually shows slight leukopenia and neutropenia. In meningitis, CSF glucose is usually normal but is occasionally between 20 and 40 mg/dL (1.1 and 2.2 mmol/L), as in bacterial meningitis. CSF protein is only mildly elevated.

Prognosis

Uncomplicated mumps usually resolves, although a relapse occurs rarely after about 2 wk. Prognosis of patients with meningitis is usually good, although permanent sequelae, such as unilateral (or rarely bilateral) nerve deafness or facial paralysis, may result. Postinfectious encephalitis, acute cerebellar ataxia, transverse myelitis, and polyneuritis occur rarely.

Treatment

• Supportive care

Treatment of mumps and its complications is supportive. The patient is isolated until glandular swelling subsides. A soft diet reduces pain caused by chewing. Acidic substances (eg, citrus fruit juices) that cause discomfort should be avoided.

Repeated vomiting due to pancreatitis may necessitate IV hydration. For orchitis, bed rest and support of the scrotum in cotton on an adhesive-tape bridge between the thighs to minimize tension or use of ice packs often relieves pain. Corticosteroids have not been shown to hasten resolution of orchitis.

Prevention

Vaccination with live mumps virus vaccine (see p. 1177 and Table 268-10 on p. 2718) provides effective prevention and causes no significant local or systemic reactions. Two doses, given as combined measles, mumps and rubella vaccine, are recommended for children; the first is given at age 12 to 15 mo, and the second at age 4 to 6 yr. Adults born during or after 1957 should have 1 dose, unless they have had mumps diagnosed by a health care practitioner. Pregnant women and people with an impaired immune system should not be given such live-attenuated vaccines.

Postexposure vaccination does not protect against mumps from that exposure. Mumps immune globulin and serum immune globulin are also not helpful.

Rubella

(German Measles; 3-Day Measles)

(See also p. 2820.)

Rubella is a contagious viral infection that may cause adenopathy, rash, and sometimes constitutional symptoms, which are usually mild and brief. Infection during early pregnancy can cause spontaneous abortion, stillbirth, or congenital defects. Diagnosis is usually clinical. Cases are reported to public health authorities Treatment is usually unnecessary. Vaccination is effective for prevention.

Rubella is caused by an RNA virus, rubella virus, which is spread by respiratory droplets through close contact or through the air. Patients can transmit rubella during asymptomatic infection or from 10 days before the rash appears until 15 days after onset of the rash. Congenitally infected infants may transmit rubella for many months after birth. Rubella is less contagious than measles. Immunity appears to be lifelong after natural infection. However, in unvaccinated populations, 10 to 15% of young adults have not had childhood infection and are susceptible. At present, incidence in the US is at a historic low because of routine childhood vaccination; all cases since 2002 have been linked to importation.

Symptoms and Signs

Many cases are mild. After a 14- to 21-day incubation period, a 1- to 5-day prodrome, usually consisting of low-grade fever, malaise, and lymphadenopathy, occurs in adults but may be minimal or absent in children. Tender swelling of the suboccipital, postauricular, and posterior cervical glands is characteristic. There is pharyngeal injection at the onset.

The rash is similar to that of measles but is less extensive and more evanescent (see Plate 64); it is often the first sign in children. It begins on the face and neck and quickly spreads to the trunk and extremities. At onset, a blanching, macular erythema may appear, particularly on the face. On the 2nd day, the rash often becomes more scarlatiniform (pinpoint) with a reddish flush. Petechiae form on the soft palate (Forschheimer's spots), later coalescing into a red blush. The rash lasts 3 to 5 days.

Constitutional symptoms in children are absent or mild and may include malaise and occasional arthralgias. Adults usually have few or no constitutional symptoms but occasionally have fever, malaise, headache, stiff joints, transient arthritis, and mild rhinitis. Fever typically resolves by the 2nd day of the rash.

Encephalitis has occurred rarely during large military outbreaks. Complete resolution is typical, but encephalitis is occasionally fatal. Thrombocytopenic purpura and otitis media occur rarely.

Diagnosis

• Clinical evaluation

• Serologic testing

Rubella is suspected in patients with characteristic adenopathy and rash. Laboratory diagnosis is necessary for pregnant women, patients with encephalitis, and neonates. Also, laboratory evaluation is strongly encouraged for all suspected cases of rubella for public health purposes. A ≥ 4-fold rise between acute and convalescent (4 to 8 wk) antibody titers confirms the diagnosis, as can serum rubella IgM antibody testing.

Differential diagnosis includes measles, scarlet fever, secondary syphilis, drug rashes, erythema

infectiosum (see p. 2840), and infectious mononucleosis as well as echovirus and coxsackievirus infections (see Table 149-7). Infections with enteroviruses and parvovirus B19 (erythema infectiosum) may be clinically indistinguishable. Rubella is differentiated from measles by the milder, more evanescent rash; milder and briefer constitutional symptoms; and absence of Koplik's spots, photophobia, and cough. Within a day of onset, scarlet fever usually causes more severe constitutional symptoms and pharyngitis than does rubella. In secondary syphilis, adenopathy is not tender, and the rash is usually prominent on the palms and soles. Also, laboratory diagnosis of syphilis is usually readily available. Infectious mononucleosis can be differentiated by its more severe pharyngitis, more prolonged malaise, and atypical lymphocytosis and by Epstein-Barr virus antibody testing (see p. 1422).

Treatment

• Supportive care

Treatment is symptomatic. No specific therapy for encephalitis is available.

Prevention

Live-virus vaccine is given routinely (see Table 268-10 on p. 2718). It produces immunity for ≥ 15 yr in > 95% of recipients and does not appear to transmit the infection. Because certain other infections are clinically indistinguishable from rubella, a reported history of rubella does not guarantee immunity.

Vaccination is given to children as combined measles, mumps and rubella vaccine in 2 doses; the first is given at age 12 to 15 mo, and the second at age 4 to 6 yr. One dose is recommended for all susceptible postpubertal people, especially college students, military recruits, health care practitioners, recent immigrants, and people working with young children. Routine vaccination is recommended for all susceptible mothers immediately after delivery. Screening women of childbearing age for rubella antibodies and immunizing those susceptible is also suggested. However, women receiving the vaccine should prevent conception for at least 28 days afterward. The vaccine virus may be capable of infecting a fetus during early pregnancy. The vaccine does not cause congenital rubella syndrome, but risk of fetal damage is estimated at ≤ 3%; *use of vaccine is contraindicated throughout pregnancy* .

Fever, rash, lymphadenopathy, polyneuropathy, arthralgia, and arthritis occur rarely after vaccination in children; painful joint swelling occasionally follows vaccination in adults, usually in women.

Progressive Rubella Panencephalitis

Progressive rubella panencephalitis is a neurologic disorder occurring in children with congenital rubella. It is presumably due to persistence or reactivation of rubella virus infection.

Some children with congenital rubella syndrome (eg, with deafness, cataracts, microcephaly, and intellectual disability) develop neurologic deficits in the early teens.

The diagnosis is considered when a child with congenital rubella develops progressive spasticity, ataxia, mental deterioration, and seizures. Testing involves at least CSF examination and serologic testing. CSF total protein and globulin and rubella antibody titers in CSF and serum are elevated. CT may show ventricular enlargement due to cerebellar atrophy and white matter disease. Brain biopsy may be necessary to exclude other causes of encephalitis or encephalopathy. Rubella virus usually cannot be recovered by viral culture or immunohistologic testing.

No specific treatment exists.

Smallpox

(Variola)

Smallpox is a highly contagious disease caused by the smallpox virus, an orthopoxvirus. It causes death in up to 30%. Indigenous infection has been eradicated. The main concern for

outbreaks is from bioterrorism. Severe constitutional symptoms and a characteristic pustular rash develop. Treatment is supportive. Prevention involves vaccination, which, because of its risks, is done selectively.

No cases of smallpox have occurred in the world since 1977 because of worldwide vaccination. In 1980, the World Health Organization (WHO) recommended discontinuation of routine smallpox vaccination. Routine vaccination in the US ended in 1972. Because humans are the only natural host of the smallpox virus and because the virus cannot survive > 2 days in the environment, WHO has declared natural infection eradicated. Recent concerns about terrorist access to existing stockpiles of smallpox virus raise the possibility of a recurrence ().

Because immunity declines over time, nearly all people—even those previously vaccinated—are now thought to be susceptible to smallpox.

Pathophysiology

There are at least 2 strains of smallpox virus. The more virulent strain causes variola major (classic smallpox); the less virulent strain causes variola minor (alastrim).

Smallpox is transmitted from person to person by direct contact or inhalation of droplet nuclei. Contaminated clothing or bed linens can also transmit infection. The infection is most communicable for the first 7 to 10 days after the rash appears. Once crusts form on the skin lesions, infectivity declines.

The attack rate is as high as 85% in unvaccinated people, and infection may lead to as many as 4 to 10 secondary cases from each primary case. However, infection tends to spread slowly and mainly among close contacts.

The virus invades the oropharyngeal or respiratory mucosa and multiplies in regional lymph nodes, causing subsequent viremia. It eventually localizes in small blood vessels of the dermis and the oropharyngeal mucosa. Other organs are seldom clinically involved, except for occasionally the CNS, with encephalitis. Secondary bacterial infection may develop in skin lesions.

Symptoms and Signs

Variola major has a 10- to 12-day incubation period (range 7 to 17 days), followed by a 2- to 3-day prodrome of fever, headache, backache, and extreme malaise. Sometimes severe abdominal pain and vomiting occur. After the prodrome, a maculopapular rash develops on the oropharyngeal mucosa, face, and arms, spreading shortly thereafter to the trunk and legs. The oropharyngeal lesions quickly ulcerate. After 1 or 2 days, the cutaneous lesions become vesicular, then pustular. Pustules are denser on the face and extremities than on the trunk, and they may appear on the palms. The pustules are round and tense and appear deeply embedded. Skin lesions of smallpox, unlike those of chickenpox, are all at the same stage of development on a given body part. After 8 or 9 days, the pustules become crusted. Severe residual scarring is typical. Mortality rate is about 30%, due to a massive inflammatory response causing shock and multiple organ failure; death usually occurs in the 2nd wk of illness.

Variola minor results in symptoms that are similar but much less severe, with a less extensive rash. Mortality rate is < 1%.

About 5 to 10% of people with smallpox develop either a hemorrhagic or a malignant variant. The hemorrhagic form is rarer and has a shorter, more intense prodrome, followed by generalized erythema and cutaneous and mucosal hemorrhage. It is uniformly fatal within 5 or 6 days. The malignant form has a similar, severe prodrome, followed by development of confluent, flat, nonpustular skin lesions. In the rare survivors, the epidermis frequently peels.

Diagnosis

• PCR

• Electron microscopy

Diagnosis is confirmed by documenting the presence of variola DNA by PCR of vesicular or pustular samples. Or the virus can be confirmed by electron microscopy or viral culture of material scraped from skin lesions (ideally, with subsequent confirmation by PCR). Suspected smallpox must be reported immediately to local public health agencies or the Centers for Disease Control and Prevention (CDC) at 770-488-7100. These agencies then arrange for testing in a laboratory with high-level containment capability (biosafety level 4).

Treatment

• Supportive care

• Isolation

• Possibly cidofovir

Treatment is generally supportive, with antibiotics for the occasional secondary bacterial infection. Antiviral drugs have never been used clinically, but cidofovir may be considered for use under an investigational new drug protocol sponsored by the CDC.

Isolation of people with smallpox is essential. In limited outbreaks, patients may be isolated in a hospital in a negative-pressure room equipped with high-efficiency particulate (HEPA) filters. In mass outbreaks, home isolation may be required. Contacts should be placed under surveillance, typically with daily temperature measurement, and isolated at home if they develop a temperature of > 38° C or other sign of illness.

Prevention

Smallpox vaccine consists of live vaccinia virus, which is related to smallpox and provides cross-immunity. Vaccine is administered with a bifurcated needle dipped in reconstituted vaccine. The needle is rapidly jabbed 15 times in an area about 5 mm in diameter and with sufficient force to draw a trace of blood. The vaccine site is covered with a dressing to prevent spread of the vaccine virus to other body sites. Fever, malaise, and myalgias are common the week after vaccination. Successful vaccination is indicated by development of a pustule by about the 7th day. Revaccination may cause only a papule surrounded by erythema, which peaks between 3 and 7 days. People without such signs of successful vaccination should be given another dose of vaccine.

Until an outbreak in the population occurs, preexposure vaccination remains recommended only for people at high risk of exposure to the virus (eg, laboratory technicians).

Vaccine complications: Risk factors for complications include extensive skin disorders (particularly eczema), immunosuppressive diseases or therapies, ocular inflammation, and pregnancy. Widespread vaccination is not recommended because of the risk. Serious complications occur in about 100 per million primary vaccines and include

• Postvaccinial encephalitis

• Progressive vaccinia

• Eczema vaccinatum

• Generalized vaccinia

Postvaccinial encephalitis occurs in about 1 of 300,000 recipients of primary vaccination, typically 8 to 15 days postvaccination.

Progressive vaccinia results in a nonhealing vaccinial (vesicular) skin lesion that spreads to adjacent skin

and ultimately other skin areas, bones, and viscera. Progressive vaccinia may occur after primary vaccination or revaccination but occurs almost exclusively in patients with an underlying defect in cell-mediated immunity; it can be fatal.

Eczema vaccinatum results in vaccinial skin lesions appearing on areas of active or even healed eczema.

Generalized vaccinia results from hematogenous dissemination of the vaccinia virus and causes vaccinia lesions at multiple body locations; it is usually benign. If there is inadvertent ocular viral implantation, vaccinia keratitis occurs rarely.

Some serious vaccine complications are treated with vaccinia immune globulin (VIG). In the past, high-risk patients who required vaccination because of viral exposure were simultaneously given VIG to try to prevent complications. The efficacy of this practice is unknown, and it is not recommended by the CDC. VIG is available only from the CDC.

Postexposure prophylaxis: Postexposure vaccination can prevent or significantly limit the severity of illness and is indicated for family members and close personal contacts of smallpox patients. Early administration is most effective, but some benefit is realized up to 4 days postexposure.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a progressive, usually fatal brain disorder occurring months to usually years after an attack of measles. It causes mental deterioration, myoclonic jerks, and seizures. Diagnosis involves EEG, CT, CSF examination, and measles serologic testing. Treatment is supportive.

SSPE is probably a persistent measles virus infection (see p.). The measles virus is present in brain tissue.

SSPE occurs in about 7 to 110 cases per million people who had wild measles and in about 1 case per million people who received measles vaccine; all cases are probably due to unrecognized measles before vaccination. Males are more often affected. Onset is usually before age 20. SSPE is exceedingly rare in the US and Western Europe.

Symptoms and Signs

Often, the first signs are subtle—diminished performance in schoolwork, forgetfulness, temper tantrums, distractibility, and sleeplessness. However, hallucinations and myoclonic jerks may then occur, followed by generalized seizures. There is further intellectual decline and speech deterioration. Dystonic movements and transient opisthotonos occur. Later, muscular rigidity, dysphagia, cortical blindness, and optic atrophy may occur. Focal chorioretinitis and other funduscopic abnormalities are common. In the final phases, hypothalamic involvement may cause intermittent hyperthermia, diaphoresis, and pulse and BP disturbances.

Diagnosis

• Serologic testing

• EEG

• Neuroimaging

SSPE is suspected in young patients with dementia and neuromuscular irritability. EEG, CT or MRI, CSF examination, and measles serologic testing are done. EEG shows periodic complexes with high-voltage diphasic waves occurring synchronously throughout the recording. CT or MRI may show cortical atrophy or white matter lesions. CSF examination usually reveals normal pressure, cell count, and total protein content; however, CSF globulin is almost always elevated, constituting up to 20 to 60% of CSF protein. Serum and CSF contain elevated levels of measles virus antibodies. Anti-measles IgG appears to

increase as the disease progresses.

If test results are inconclusive, brain biopsy may be needed.

Prognosis

The disease is almost invariably fatal within 1 to 3 yr (often pneumonia is the terminal event), although some patients have a more protracted course. A few patients have remissions and exacerbations.

Treatment

• Supportive care

Anticonvulsants and other supportive measures are the only accepted treatments. Isoprinosine, interferon alfa, and lamivudine are controversial, and antiviral drugs have generally not proved helpful.

Chapter 156. Sexually Transmitted Diseases

Introduction

Sexually transmitted diseases (STDs), also termed sexually transmitted infections (STIs), can be caused by a number of microorganisms that vary widely in size, life cycle, symptoms, and susceptibility to available treatments.

Bacterial STDs include syphilis, gonorrhea, chancroid, lymphogranuloma venereum, granuloma inguinale, and chlamydial, mycoplasmal, and *Ureaplasma* infections.

Viral STDs include genital and anorectal warts, genital herpes (see p. <u>1418</u>), molluscum contagiosum (see p. <u>715</u>), and HIV infection (see p. <u>1438</u>).

Parasitic infections that can be sexually transmitted include trichomoniasis (caused by protozoa), scabies (caused by mites—see p. <u>713</u>), and pediculosis pubis (caused by lice—see p. <u>713</u>).

Many other infections not considered primarily to be STDs—including salmonellosis, shigellosis, campylobacteriosis, amebiasis, giardiasis, hepatitis (A, B, and C), and cytomegalovirus infection—can be transmitted sexually.

Because sexual activity includes close contact with skin and mucous membranes of the genitals, mouth, and rectum, many organisms are efficiently spread between people. Inflammation or ulceration caused by some STDs (eg, herpes, chancroid) predisposes to transmission of others (eg, HIV). STD prevalence rates remain high in most of the world, despite diagnostic and therapeutic advances that can rapidly render patients with many STDs noninfectious. Factors impeding control of STDs include

• Unprotected sexual activity with multiple partners

• Difficulty talking about sexual issues for both physicians and patients

• Inadequate funding for new therapy and research

• Susceptibility to reinfection if both partners are not treated simultaneously

• Incomplete treatment, which leads to development of drug-resistant organisms

• International travel, which facilitates rapid global dissemination of STDs

Symptoms and signs vary depending on the infection. Many STDs cause genital lesions (see <u>Table 156-1</u>).

STDs are diagnosed and treated in a variety of settings; for many, diagnostic tests are limited or unavailable or patient follow-up is uncertain. Thus, identification of the causative organism is often not pursued, and initial treatment is often syndromic—ie, directed at the organisms most likely to cause the presenting syndrome (eg, urethritis, cervicitis, genital ulcers, pelvic inflammatory disease). Diagnostic testing is done more often when the diagnosis is unclear, when the infection is severe, when initial treatment is ineffective, or when other reasons (eg, public health surveillance, psychosocial reasons, including extreme mental distress and depression) are compelling.

STD control depends on

• Adequate facilities and personnel for diagnosis and treatment

• Public health programs for locating and treating recent sex partners of patients

• Follow-up for treated patients to ensure that they have been cured

• Education of health care practitioners and the public

• Avoidance of high-risk behaviors by patients

[**Table 156-1.** Differentiating Common Sexually Transmitted Genital Lesions]

Condoms and vaginal dams, if used correctly, greatly decrease risk. Vaccines are unavailable for most STDs, except for hepatitis A and B and human papillomavirus infection.

Chancroid

Chancroid is infection of the genital skin or mucous membranes caused by *Haemophilus ducreyi* and characterized by papules, painful ulcers, and enlargement of the inguinal lymph nodes leading to suppuration. Diagnosis is usually clinical because culturing the organism is difficult. Treatment is with a macrolide, ceftriaxone, or ciprofloxacin.

H. ducreyi is a short, slender, gram-negative bacillus with rounded ends. Chancroid occurs in rare outbreaks in developed countries but is a common cause of genital ulcers throughout much of the developing world and often acquired by men from prostitutes. Like other sexually transmitted diseases (STDs) causing genital ulcers, chancroid increases risk of HIV transmission.

Symptoms and Signs

After an incubation period of 3 to 7 days, small, painful papules appear and rapidly break down into shallow, soft, painful ulcers with ragged, undermined edges (ie, with overhanging tissue) and a red border. Ulcers vary in size and often coalesce. Deeper erosion occasionally leads to marked tissue destruction. The inguinal lymph nodes become tender, enlarged, and matted together, forming a pusfilled abscess (bubo). The skin over the abscess may become red and shiny and may break down to form a sinus. The infection may spread to other areas of skin, resulting in new lesions. Phimosis, urethral stricture, and urethral fistula may result from chancroid.

Diagnosis

• Clinical evaluation

• Sometimes culture or PCR

Chancroid is suspected in patients who have unexplained genital ulcers or buboes (which may be mistaken for abscesses) and who have been in endemic areas. Genital ulcers with other causes (see Table 156-1) may resemble chancroid.

If available, a sample of pus from a bubo or exudate from the edge of an ulcer should be sent to a laboratory that can identify *H. ducreyi*. However, diagnosis is usually based on clinical findings alone because culture of the bacteria is difficult and microscopic identification is confounded by the mixed flora in ulcers. PCR testing has a high sensitivity (98.4%) and a high specificity (99.6%) for *H. ducreyi* but is not widely available. Clinical diagnosis has a lower sensitivity (53 to 95%) and specificity (41 to 75%).

Serologic testing for syphilis and HIV and cultures for herpes should be done to exclude other causes of genital ulcers. However, interpretation of test results is complicated by the fact that genital ulcers due to other causes may be co-infected with *H. ducreyi*.

Treatment

• Antibiotics (various)

Treatment should be started promptly, without waiting for test results. One of the following is recommended:

• A single-dose of azithromycin 1 g po or ceftriaxone 250 mg IM

• Erythromycin 500 mg po qid for 7 days

• Ciprofloxacin 500 mg po bid for 3 days

Patients treated for other causes of genital ulcers should be given antibiotics that also treat chancroid if chancroid is suspected and laboratory testing is impractical. Treatment of patients with HIV infection, particularly with single-dose regimens, may be ineffective.

Buboes can safely be aspirated for diagnosis or incised for symptomatic relief if patients are also given effective antibiotics. Sex partners should be examined, and patients should be followed for 3 mo.

Chlamydial, Mycoplasmal, and Ureaplasmal Infections

Sexually transmitted urethritis, cervicitis, proctitis, and pharyngitis not due to gonorrhea are caused predominantly by chlamydiae and infrequently by mycoplasmas or *Ureaplasma* sp. Chlamydiae may also cause salpingitis, epididymitis, perihepatitis, neonatal conjunctivitis, and infant pneumonia. Untreated chlamydial salpingitis can become chronic, causing minimal symptoms but having serious consequences. Diagnosis is by culture, immunoassay for antigens, or genetic methods. Treatment is with single-dose azithromycin or a week of ofloxacin, levofloxacin, erythromycin, or a tetracycline.

Several organisms can cause nongonococcal sexually transmitted cervicitis in women and urethritis, proctitis, and pharyngitis in both sexes. These organisms include *Chlamydia trachomatis* (responsible for about 50% of such cases of urethritis and most cases of mucopurulent cervicitis), *Mycoplasma genitalium, Ureaplasma urealyticum*, and *Trichomonas vaginalis* (see p.). Chlamydiae may also cause lymphogranuloma venereum (see p.). The imprecise terms nonspecific "urethritis" and "nongonococcal urethritis" have been replaced by terms that specify the causative organism.

Symptoms and Signs

Men develop symptomatic urethritis after a 7- to 28-day incubation period, usually beginning with mild dysuria, discomfort in the urethra, and a clear to mucopurulent discharge. Discharge may be slight, and symptoms may be mild but are frequently more marked early in the morning; then, the urethral meatus is often red and blocked with dried secretions, which may also stain underclothes. Occasionally, onset is more acute, with dysuria, frequency, and a copious, purulent discharge that simulates gonococcal urethritis. Infection may progress to epididymitis. After rectal or orogenital contact with an infected person, proctitis or pharyngitis may develop.

Women are usually asymptomatic, although vaginal discharge, dysuria, increased urinary frequency and urgency, pelvic pain, dyspareunia, and symptoms of urethritis may occur. Cervicitis with yellow, mucopurulent exudate and cervical ectopy (expansion of the red endocervical epithelium onto the vaginal surfaces of the cervix) are characteristic. Pelvic inflammatory disease (salpingitis and pelvic peritonitis) may cause lower abdominal discomfort (typically bilateral) and marked tenderness when the abdomen, adnexa, and cervix are palpated. Fitz-Hugh-Curtis syndrome (perihepatitis) may cause right upper quadrant pain, fever, and vomiting.

Chlamydiae may be transferred to the eye, causing acute conjunctivitis.

Reactive arthritis (see p.) caused by immunologic reactions to genital and intestinal infections is an infrequent complication of chlamydial infections in adults. Reactive arthritis sometimes causes skin and eye lesions and noninfectious recurrent urethritis.

Infants born to women with chlamydial cervicitis may develop chlamydial pneumonia or ophthalmia neonatorum (neonatal conjunctivitis—see p.).

Diagnosis

• Nucleic acid detection tests of cervical or urethral exudate or urine

Chlamydial, mycoplasmal, or ureaplasmal infection is suspected in patients with symptoms of urethritis, salpingitis, cervicitis, or unexplained proctitis, but similar symptoms can also result from gonococcal infection. If clinical evidence for urethritis is uncertain, finding ≥ 5 WBCs/high-power field in a urine sample confirms the diagnosis. Examination of first-voided, morning samples is most sensitive.

Samples of cervical or male urethral exudates are obtained to check for chlamydia. Nucleic acid-based tests (NAT) for chlamydial DNA may be done on nonamplified samples or may use one of several nucleic acid amplification techniques. Tests are usually done on swab samples, but amplified NAT tests are highly sensitive and specific and can also be done on urine, eliminating the need for doing an uncomfortable swab of the urethra or cervix. Amplification techniques should be routinely used in patients at high risk (eg, unprotected sex with new or multiple partners, history of prior sexually transmitted disease [STD], exchanging sex for drugs or money). Because gonococcal infection sometimes coexists, testing should also be done for that organism.

Detection of mycoplasmas and *Ureaplasma* sp is currently impractical in routine practice.

In the US, confirmed cases of chlamydial infection, gonorrhea, and syphilis must be reported to the public health system. A serologic test for syphilis (STS) should be done.

Screening: Urine testing using nucleic acid amplification tests (NAAT) is especially useful for screening asymptomatic people at high risk of STDs because genital examination is not necessary. People who should be screened include

• People with a history of a previous STD

• People with high-risk behaviors

• Sexually active adolescents and young adults < 24 yr

• Pregnant women < 24 yr

Treatment

• Oral antibiotics (various)

• Treatment of sex partners

Uncomplicated documented or suspected chlamydial, ureaplasmal, or mycoplasmal infections are treated with one of the following:

• A single dose of azithromycin 1 g po

• Doxycycline 100 mg po bid for 7 days

• Erythromycin base 500 mg po qid for 7 days

• Ofloxacin 300 mg po bid for 7 days

• Levofloxacin 500 mg po once/day for 7 days

For pregnant women, azithromycin 1 g po once should be used.

These regimens do not reliably treat gonorrhea, which coexists in many patients with chlamydial infections. Therefore, treatment should usually include a cephalosporin, such as a single dose of ceftriaxone 125 mg IM.

Patients who relapse (about 10%) are usually coinfected with microbes that do not respond to antichlamydial therapy, or they were rein-fected since treatment. They may require further diagnostic evaluation and repeated or longer (21 to 28 days) courses, and their current sex partners should be treated. Patients should abstain from sexual intercourse until they and their partners complete treatment.

If chlamydial genital infections are untreated, symptoms and signs subside within 4 wk in about two thirds of patients. However, in women, asymptomatic cervical infection may persist, resulting in chronic endometritis, salpingitis, or pelvic peritonitis and their sequelae—pelvic pain, infertility, and increased risk of ectopic pregnancy. Because chlamydial infections can have serious long-term consequences for women, even when symptoms are mild or absent, detecting the infection in women and treating them and their male sex partners is crucial.

Genital Warts

(Condylomata Acuminata; Venereal Warts; Anogenital Warts)

Genital warts are lesions of the skin or mucous membranes of the genitals caused by certain types of human papillomavirus (HPV). Some types of HPV cause flat warts in the cervical canal or anus; these warts can become cancerous. Diagnosis of external warts is based on their clinical appearance. Multiple treatments exist, but few are highly effective unless applied repeatedly over weeks to months. Genital warts may resolve without treatment in immunocompetent patients but may persist and spread in patients with decreased cell-mediated immunity (eg, due to pregnancy or HIV infection).

In the US, an estimated 1.4 million people have genital warts at any given time. There are about 6 million new cases of genital HPV infection each year, and about 80% of women have been infected at least once by age 50. Most infections clear spontaneously within 1 to 2 yr, but some persist.

Etiology

There are > 70 known types of HPV. Some types cause common skin warts (see p. 715), but others infect primarily the skin and mucosa of the anogenital region. Important manifestations of anogenital HPV include

• Genital warts (condyloma acuminatum)

• Intraepithelial neoplasia and carcinoma of the cervix, anus, or penis

• Bladder and oral cancers

• Bowenoid papulosis

Condylomata acuminata are benign anogenital warts most often caused by HPV types 6 and 11. Low- and high-grade intraepithelial neoplasia and carcinoma may be caused by HPV types 16 and 18 and probably other types.

HPV is transmitted from lesions during skin-to-skin contact. The types that affect the anogenital region are usually transmitted sexually by penetrative vaginal or anal intercourse, but digital, oral, and nonpenetrative genital contact may be involved.

Genital warts are more common among immunocompromised patients. Growth rates vary, but pregnancy, immunosuppression, or maceration of the skin may accelerate the growth and spread of warts.

Symptoms and Signs

Warts appear after an incubation period of 1 to 6 mo. Visible anogenital warts are usually soft, moist, minute pink or gray polyps (raised lesions) that enlarge, may become pedunculated, have rough surfaces,

and may occur in clusters. They are usually asymptomatic, but some patients have itching, burning, or discomfort.

In men, warts occur most commonly under the foreskin, on the coronal sulcus, within the urethral meatus, and on the penile shaft. They may occur around the anus and in the rectum, especially in homosexual men. In women, warts occur most commonly on the vulva, vaginal wall, cervix, and perineum; the urethra and anal region may be affected. HPV types 16 and 18 usually cause flat endocervical or anal warts that are difficult to see and diagnose clinically.

Diagnosis

• Clinical evaluation, sometimes including colposcopy, anoscopy, or both

Genital warts are usually diagnosed clinically. Their appearance usually differentiates them from condyloma lata of secondary syphilis, which are flat-topped. However, serologic tests for syphilis (STS) should be done initially and after 3 mo. Biopsies of atypical, bleeding, ulcerated, or persistent warts may be necessary to exclude carcinoma. Endocervical and anal warts can be visualized only by colposcopy and anoscopy. Applying a 3 to 5% solution of acetic acid for a few minutes before colposcopy causes warts to whiten and enhances visualization and detection of small warts. Nucleic acid amplification tests (NAAT) for HPV DNA confirm the diagnosis and allow typing of HPV, but their role in HPV management is not yet clear.

Treatment

• Manual removal (eg, by cryotherapy, electro-cauterization, laser, or surgical excision)

• Topical treatment (eg, with antimitotics, caustics, or interferon inducers)

No treatment of anogenital warts is completely satisfactory, and relapses are frequent and require retreatment. In immunocompetent people, genital warts may resolve without treatment. In immunocompromised patients, warts may be less responsive to treatment.

Genital warts may be removed by cryotherapy, electro-cauterization, laser, or surgical excision; a local or general anesthetic is used depending on the size and number to be removed. Removal with a resectoscope may be the most effective treatment; a general anesthetic is used.

Topical antimitotics (eg, podophyllotoxin, podophyllin, 5-fluorouracil), caustics (eg, trichloroacetic acid), and interferon inducers (eg, imiquimod) are widely used but usually require multiple applications over weeks to months and are frequently ineffective. Before topical treatments are applied, surrounding tissue should be protected with petroleum jelly. Patients should be warned that after treatment, the area may be painful.

Interferon alfa (eg, interferon alfa-2b, interferon alfa-n3), intralesionally or IM, has cleared intractable lesions on the skin and genitals, but optimal administration and long-term effects are unclear. Also, in some patients with bowenoid papulosis of the genitals (caused by type 16 HPV), lesions initially disappeared after treatment with interferon alfa but reappeared as invasive cancers.

For intraurethral lesions, thiotepa (an alkylating drug), instilled in the urethra, is effective. In men, 5-fluorouracil applied bid to tid is highly effective for urethral lesions, but rarely, it causes swelling, leading to urethral obstruction. Endocervical lesions should not be treated until Papanicolaou (Pap) test results rule out other cervical abnormalities (eg, dysplasia, cancer) that may dictate additional treatment.

By removing the moist underside of the prepuce, circumcision may prevent recurrences in uncircumcised men.

Sex partners of women with endocervical warts and of patients with bowenoid papulosis should be counseled and screened regularly for HPV-related lesions. A similar approach can be used for HPV in the rectum.

Current sex partners of people with genital warts should be examined and, if infected, treated.

Prevention

A quadrivalent vaccine that protects against the 2 types of HPV (types 6 and 11) that cause > 90% of visible genital warts is available. This vaccine also protects against the 2 types of HPV (types 16 and 18) that cause most cervical cancers. The HPV vaccine has been recommended for girls and women aged 9 to 26 yr for prevention of initial infection. Three doses are given, preferably at age 11 to 12 yr. The vaccine should be administered before onset of sexual activity, but girls and women who are sexually active should still be vaccinated. The vaccine's role in preventing HPV in boys and men has not been established. A bivalent vaccine against HPV types 16 and 18 is awaiting approval.

Because of the location of these warts, condoms may not fully protect against infection.

Gonorrhea

Gonorrhea is caused by the bacteria *Neisseria gonorrhoeae*. It typically infects epithelia of the urethra, cervix, rectum, pharynx, or eyes, causing irritation or pain and purulent discharge. Dissemination to skin and joints, which is uncommon, causes sores on the skin, fever, and migratory polyarthritis or pauciarticular septic arthritis. Diagnosis is by microscopy, culture, or nucleic acid amplification tests. Several oral or injectable antibiotics can be used, but drug resistance is an increasing problem.

N. gonorrhoeae occurs only in humans and is almost always transmitted by sexual contact. Urethral and cervical infections are most common, but infection in the pharynx or rectum can occur after oral or anal intercourse, and conjunctivitis may follow contamination of the eye. After an episode of vaginal intercourse, likelihood of transmission from women to men is about 20%, but from men to women, it may be higher. Neonates can acquire conjunctival infection during passage through the birth canal (see p.), and children may acquire gonorrhea as a result of sexual abuse.

In 10 to 20% of women, cervical infection ascends via the endometrium to the fallopian tubes (salpingitis) and pelvic peritoneum, causing pelvic inflammatory disease (PID—see p.). Chlamydiae or intestinal bacteria may also cause PID. Gonorrheal cervicitis is commonly accompanied by dysuria or inflammation of Skene's ducts and Bartholin's glands. In a small fraction of men, ascending urethritis progresses to epididymitis. Disseminated gonococcal infection (DGI) due to hematogenous spread occurs in < 1% of cases, predominantly in women. DGI typically affects the skin, tendon sheaths, and joints. Pericarditis, endocarditis, meningitis, and perihepatitis occur rarely.

Coinfection with *Chlamydia trachomatis* occurs in 15 to 25% of infected heterosexual men and 35 to 50% of women.

Symptoms and Signs

About 10 to 20% of infected women and very few infected men are asymptomatic. About 25% of men have minimal symptoms.

Male urethritis has an incubation period from 2 to 14 days. Onset is usually marked by mild discomfort in the urethra, followed by more severe penile tenderness and pain, dysuria, and a purulent discharge. Urinary frequency and urgency may develop as the infection spreads to the posterior urethra. Examination detects a purulent, yellow-green urethral discharge, and the meatus may be inflamed.

Epididymitis usually causes unilateral scrotal pain, tenderness, and swelling. Rarely, men develop abscesses of Tyson's and Littre's glands, periurethral abscesses, or infection of Cowper's glands, the prostate, or the seminal vesicles.

Cervicitis usually has an incubation period of > 10 days. Symptoms range from mild to severe and include dysuria and vaginal discharge. During pelvic examination, clinicians may note a mucopurulent or

purulent cervical discharge, and the cervical os may be red and bleed easily when touched with the speculum. Urethritis may occur concurrently; pus may be expressed from the urethra when the symphysis pubis is pressed or from Skene's ducts or Bartholin's glands. Rarely, infections in sexually abused prepubertal girls cause dysuria, purulent vaginal discharge, and vulvar irritation, erythema, and edema.

PID occurs in 10 to 20% of infected women. PID may include salpingitis, pelvic peritonitis, and pelvic abscesses and may cause lower abdominal discomfort (typically bilateral), dyspareunia, and marked tenderness on palpation of the abdomen, adnexa, or cervix.

Fitz-Hugh-Curtis syndrome is gonococcal (or chlamydial) perihepatitis that occurs predominantly in women and causes right upper quadrant abdominal pain, fever, nausea, and vomiting, often mimicking biliary or hepatic disease.

Rectal gonorrhea is usually asymptomatic. It occurs predominantly in men practicing receptive anal intercourse and can occur in women who participate in anal sex. Symptoms include rectal itching, a cloudy rectal discharge, bleeding, and constipation—all of varying severity. Examination with a proctoscope may detect erythema or mucopurulent exudate on the rectal wall.

Gonococcal pharyngitis is usually asymptomatic but may cause sore throat. *N. gonorrhoeae* must be distinguished from *N. meningitidis*, a closely related organism that is often present in the throat without causing symptoms or harm.

Disseminated gonococcal infection (DGI), also called the arthritis-dermatitis syndrome, reflects bacteremia and typically manifests with fever, migratory pain or joint swelling (polyarthritis), and pustular skin lesions (see Plate 59). In some patients, pain develops and tendons (eg, at the wrist or ankle) redden or swell. Skin lesions occur typically on the arms or legs, have a red base, and are small, slightly painful, and often pustular. Genital gonorrhea, the usual source of disseminated infection, may be asymptomatic. DGI can mimic other disorders that cause fever, skin lesions, and polyarthritis (eg, the prodrome of hepatitis B infection or meningococcemia); some of these disorders may cause genital symptoms (eg, reactive arthritis—see p.).

Gonococcal septic arthritis is a more focal form of DGI that results in a painful arthritis with effusion, usually of 1 or 2 large joints such as the knees, ankles, wrists, or elbows. Some patients used to have or still have skin lesions of DGI. Onset is often acute, usually with fever, severe joint pain, and limitation of movement. Infected joints are swollen, and the overlying skin may be warm and red.

Diagnosis

• Gram staining and culture

• Nucleic acid-based testing

Gonorrhea is diagnosed when gonococci are detected via microscopic examination using Gram stain, culture, or a nucleic acid-based test of genital fluids, blood, or joint fluids (obtained by needle aspiration).

Gram stain is sensitive and specific for gonorrhea in men with urethral discharge; gram-negative intracellular diplococci typically are seen. Gram stain is much less accurate for infections of the cervix, pharynx, and rectum and is not recommended for diagnosis at these sites.

Culture is sensitive and specific, but because gonococci are fragile and fastidious, samples taken using a swab need to be rapidly plated on an appropriate medium (eg, modified Thayer-Martin) and transported to the laboratory in a CO_2-containing environment. Blood and joint fluid samples should be sent to the laboratory with notification that gonococcal infection is suspected.

Unamplified **nucleic acid-based tests** may be done on genital rectal or oral swabs. Most tests simultaneously detect gonorrhea and chlamydial infection and then differentiate between them in a subsequent specific test. Nucleic acid amplification tests (NAAT) further increase the sensitivity

adequately to enable testing of urine samples in both sexes.

In the US, confirmed cases of gonorrhea, chlamydial infection and syphilis must be reported to the public health system. A serologic test for syphilis (STS) and a screening test for chlamydial infection should be done.

Men with urethritis: Men with obvious discharge may be treated presumptively if likelihood of follow-up is questionable or if clinic-based diagnostic tools are not available. Samples for Gram staining can be obtained by touching a swab or slide to the end of the penis to collect discharge. Gram stain does not identify chlamydiae, so urine or swab samples for NAAT are obtained.

Women with genital symptoms or signs: A cervical swab should be sent for culture or nucleic acid-based testing. If a pelvic examination is not possible, NAAT of a urine sample can detect gonococcal (and chlamydial) infections rapidly and reliably.

Pharyngeal or rectal exposures (either sex): Swabs of the affected area are sent for culture or nucleic acid-based tests.

Arthritis, DGI, or both: An affected joint should be aspirated, and fluid should be sent for culture and routine analysis (see p. 286) Patients with skin lesions, systemic symptoms, or both should have blood, urethral, cervical, and rectal cultures or NAAT. In about 30 to 40% of patients with DGI, blood cultures are positive during the first week of illness. With gonococcal arthritis, blood cultures are less often positive, but cultures of joint fluids are usually positive. Joint fluid is usually cloudy to purulent because of large numbers of WBCs (typically > 20,000/μL).

Screening: Asymptomatic patients considered at high risk of sexually transmitted diseases (STDs) can be screened by NAAT of urine samples, thus not requiring invasive procedures to collect samples from genital sites. Patients at risk include

• People with a history of a previous STD

• People with high-risk behaviors (eg, new or multiple sex partners, inconsistent use of condoms, exchange of sex for money or drugs)

• Sexually active adolescents and young adults < 24 yr

• Pregnant women < 24 yr

Treatment

• For uncomplicated infection, a single dose of ceftriaxone or cefixime

• For DGI with arthritis, a longer course of parenteral antibiotics

• Concomitant treatment for chlamydial infection

• Treatment of sex partners

Uncomplicated gonococcal infection of the urethra, cervix, rectum, and pharynx can be treated with a single dose of ceftriaxone 125 mg IM or cefixime 400 mg po. Previous alternative regimens with quinolones (eg, ciprofloxacin, levofloxacin, ofloxacin) are no longer recommended because of increasing drug resistance. Routinely, patients are simultaneously given a single dose of azithromycin 1 g po to treat chlamydial infection (see p. 1469) because it often coexists in patients with gonorrhea.

DGI with gonococcal arthritis is initially treated with IM or IV antibiotics (eg, ceftriaxone 1 g IM or IV q 24 h, ceftizoxime 1 g IV q 8 h, cefotaxime 1 g IV q 8 h) continued for 24 to 48 h once symptoms lessen, followed by 4 to 7 days of oral therapy. Antichlamydial therapy is also routinely given.

Gonococcal arthritis does not usually require joint drainage. Initially, the joint is immobilized in a functional position. Passive range-of-motion exercises should be started as soon as patients can tolerate them. Once pain subsides, more active exercises, with stretching and muscle strengthening, should begin. Over 95% of patients treated for gonococcal arthritis recover complete joint function. Because sterile joint fluid accumulations (effusions) may persist for prolonged periods, an anti-inflammatory drug may be beneficial.

Posttreatment cultures are unnecessary if symptomatic response is adequate. However, for patients with symptoms for > 7 days, cultures are repeated, and antimicrobial sensitivity testing is done. Patients should abstain from sexual activity until treatment is completed to avoid infecting sex partners.

Sex partners: All sex partners who have had sexual contact with the patient within 60 days should be tested for gonorrhea and other STDs and treated if results are positive. Sex partners with contact within 2 wk should be treated presumptively for gonorrhea (epidemiologic treatment).

Expedited partner therapy (EPT) involves giving patients a prescription or drugs to deliver to their partner. EPT may enhance partner adherence and reduce treatment failure due to reinfection. It may be most appropriate for partners of women with gonorrhea or chlamydial infection. However, a health care visit is preferable to ascertain histories of drug allergies and to screen for other STDs.

Granuloma Inguinale

(Donovanosis)

Granuloma inguinale is a progressive infection of genital skin caused by *Calymmatobacterium granulomatis*. Skin lesions are beefy red, raised, and often ulcerated. Diagnosis is by clinical criteria and microscopy. Treatment is with antibiotics, usually tetracyclines, macrolides, or trimethoprim/sulfamethoxazole.

The bacteria *Calymmatobacterium* (formerly *Donovania*) *granulomatis* are very rare in most of the world. Current epidemiologic data are unavailable, but historically, granuloma inguinale has been reported in areas such as Papua New Guinea, northern Australia, southern Africa, and parts of Brazil and India.

Symptoms and Signs

Sites of infection are

• Penis, scrotum, groin, and thighs in men (see
Plate 63)

• Vulva, vagina, and perineum in women (see
Plate 62)

• Anus and buttocks in patients who engage in anal-receptive intercourse

• Face in both sexes

After an incubation period of about 1 to 12 wk, a painless, red skin nodule slowly enlarges, becoming a raised, beefy red, moist, smooth, foul-smelling lesion. The lesion slowly enlarges and may spread to other skin areas. Lesions heal slowly, with scarring. Secondary infections with other bacteria are common and can cause extensive tissue destruction.

Occasionally, granuloma inguinale spreads through the bloodstream to the bones, joints, or liver; without treatment, anemia, wasting, and uncommonly death may occur.

Diagnosis

• Microscopic examination showing Donovan bodies in fluid from a lesion

Granuloma inguinale is suspected in patients from endemic areas with characteristic lesions. Diagnosis is confirmed microscopically by the presence of Donovan bodies (numerous bacilli in the cytoplasm of macrophages shown by Giemsa or Wright's stain) in smears of fluid from scrapings from the edge of lesions. These smears contain many plasma cells. Biopsy specimens are taken if the diagnosis is unclear or if adequate tissue fluid cannot be obtained because lesions are dry, sclerotic, or necrotic. The bacteria do not grow on ordinary culture media.

Treatment

• Antibiotics (various)

Many oral antibiotics kill the bacteria, but tetracyclines, macrolides, and trimethoprim/sulfamethoxazole (TMP/SMX) are most effective, followed by ceftriaxone, aminoglycosides, fluoroquinolones, and chloramphenicol. Recommended oral regimens include doxycycline 100 mg bid for 3 wk, TMP/SMX 160/800 mg bid for 3 wk, erythromycin 500 mg qid for 3 wk, or azithromycin 1 g/wk for 3 wk. IV or IM antibiotics (eg, ceftriaxone) are an alternative.

Response to treatment should begin within 7 days, but healing of extensive disease may be slow and lesions may recur, requiring longer treatment. HIV-infected patients may also require prolonged or intensive treatment. After apparently successful treatment, follow-up should continue for 6 mo. Current sex partners should be examined and, if infected, treated.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is a chlamydial disease characterized by a small, often asymptomatic skin lesion, followed by regional lymphadenopathy in the groin or pelvis or by proctitis in homosexual men. Without treatment, LGV may cause obstruction of lymph flow and chronic swelling of genital tissues. Diagnosis is by clinical signs, but laboratory confirmation with serologic or immunofluorescent testing is usually possible. Treatment is 21 days of a tetracycline or erythromycin.

LGV is caused by serotypes L1, L2, and L3 of the bacteria *Chlamydia trachomatis*. These serotypes differ from those that cause trachoma, inclusion conjunctivitis, urethritis, and cervicitis because they can invade and reproduce in regional lymph nodes.

LGV occurs sporadically in the US but is endemic in parts of Africa, India, Southeast Asia, South America, and the Caribbean. It is diagnosed much more often in men than women.

Symptoms and Signs

The 1st stage begins after an incubation period of about 3 days with a small skin lesion at the site of entry. It may cause the overlying skin to break down (ulcerate) but heals so quickly that it may pass unnoticed.

The 2nd stage usually begins in men after about 2 to 4 wk, with the inguinal lymph nodes on one or both sides enlarging and forming large, tender, sometimes fluctuant masses (buboes). The buboes stick to deeper tissues and cause the overlying skin to become inflamed, sometimes with fever and malaise. In women, backache or pelvic pain is common; the initial lesions may be on the cervix or upper vagina, resulting in enlargement and inflammation of deeper perirectal and pelvic lymph nodes. Multiple draining sinus tracts may develop and discharge pus or blood.

In the 3rd stage, lesions heal with scarring, but sinus tracts can persist or recur. Persistent inflammation due to untreated infection obstructs the lymphatic vessels, causing swelling and skin sores.

In homosexual men, proctitis or proctocolitis with bloody purulent rectal discharges may occur in the 1st stage. In the chronic stages, colitis simulating Crohn's disease may cause tenesmus and strictures in the rectum or pain due to inflamed pelvic nodes.

Diagnosis

• Antibody detection

LGV is suspected in patients who have genital ulcers, swollen inguinal lymph nodes, or proctitis and who live in, have visited, or have sexual contact with people from areas where infection is common. LGV is also suspected in patients with buboes, which may be mistaken for abscesses caused by other bacteria.

Diagnosis has usually been made by detecting antibodies to chlamydial endotoxin; levels are usually elevated at presentation or shortly thereafter and remain elevated. Direct tests for chlamydial antigens with immunoassays (eg, enzyme-linked immunosorbent assay [ELISA]) or with immunofluorescence using monoclonal antibodies to stain pus or nucleic acid amplification tests may be available through reference laboratories (eg, Centers for Disease Control and Prevention in the US).

All sex partners should be evaluated. After apparently successful treatment, patients should be followed for 6 mo.

Treatment

• Oral tetracyclines or erythromycin

• Possibly drainage of buboes for symptomatic relief

Doxycycline 100 mg po bid, erythromycin 500 mg po qid, or tetracycline 500 mg po qid, each for 21 days, are effective for early disease. Azithromycin 1 g po once/wk for 1 to 3 wk is probably effective, but neither it nor clarithromycin has been adequately evaluated.

Swelling of damaged tissues in later stages may not resolve despite elimination of the bacteria. Buboes may be drained by needle or surgically if necessary for symptomatic relief, but most patients respond quickly to antibiotics. Buboes and sinus tracts may require surgery, but rectal strictures can usually be dilated.

Sexually Transmitted Enteric Infections

Various pathogens—bacterial (*Shigella, Campylobacter*, or *Salmonella*), viral (hepatitis A, B, and C viruses), and parasitic (*Giardia* sp or amebae)—are transmitted via sexual practices, especially those that can involve fecal-oral contamination. In order of decreasing risk, these practices are oral-rectal, anal-genital, oral-genital, and genital-genital intercourse.

Although some of the above pathogens may cause proctitis, they usually cause infection higher in the intestinal tract; symptoms include diarrhea, fever, bloating, nausea, and abdominal pain. Multiple infections are frequent, especially in people with many sex partners. Most of these pathogens can cause infections without symptoms; asymptomatic infections are the rule with *Entamoeba dispar*, which commonly occurs in homosexual men and was previously known as nonpathogenic *Entamoeba histolytica*. For diagnosis and treatment of these infections, see elsewhere in THE MANUAL.

Syphilis

(See also Congenital Syphilis on p. 2821.)

Syphilis is caused by the spirochete *Treponema pallidum* and is characterized by 3 sequential clinical, symptomatic stages separated by periods of asymptomatic latent infection. Common manifestations include genital ulcers, skin lesions, meningitis, aortic disease, and neurologic syndromes. Diagnosis is by serologic tests and adjunctive tests selected based on the disease stage. Penicillin is the drug of choice.

Syphilis is caused by *T. pallidum*, a spirochete that cannot survive for long outside the human body. *T. pallidum* enters through the mucous membranes or skin, reaches the regional lymph nodes within hours,

and rapidly spreads throughout the body.

Syphilis occurs in primary, secondary, and tertiary stages (see
Table 156-2), with long latent periods between them. Infected people are contagious during the first 2 stages.

Infection is usually transmitted by sexual contact (including genital, orogenital, and anorectal) but may be transmitted non-sexually by skin contact or transplacentally (see p. 2821). Risk of transmission is about 30% from a single sexual encounter with a person who has primary syphilis and 60 to 80% from an infected mother to a fetus. Infection does not lead to immunity against reinfection.

Symptoms and Signs

Syphilis may manifest at any stage and may affect multiple or single organs, mimicking many other disorders. Syphilis may be accelerated by coexisting HIV infection; in these cases, eye involvement, meningitis, and other neurologic complications are more common and more severe.

Primary syphilis: After an incubation period of 3 to 4 wk (range 1 to 13 wk), a primary lesion (chancre —see
Plate 66) develops at the site of inoculation. The initial red papule quickly forms a chancre, usually a painless ulcer with a firm base; when rubbed, it produces clear fluid containing numerous spirochetes. Nearby lymph nodes may be enlarged, firm, and nontender. Chancres can occur anywhere but are most common on the following:

• Penis, anus, and rectum in men

• Vulva, cervix, rectum, and perineum in women

• Lips or mouth in either sex

Secondary syphilis: The spirochete spreads in the bloodstream, producing widespread mucocutaneous lesions (see
Plate 67), lymph

[**Table 156-2.** Classification of Syphilis]

node swelling, and, less commonly, symptoms in other organs. Symptoms typically begin 6 to 12 wk after the chancre appears; about 25% of patients still have a chancre. Fever, loss of appetite, nausea, and fatigue are common. Headache, hearing or balance problems, visual disturbances, and bone pain can also occur.

Over 80% of patients have mucocutaneous lesions; a wide variety of rashes and lesions occur, and any body surface can be affected. Without treatment, lesions may disappear in a few days to weeks, persist for months, or return after healing, but all eventually heal, usually without scarring.

Syphilitic dermatitis is usually symmetric and more marked on the palms and soles. The individual lesions are round, often scale, and may coalesce to produce larger lesions, but they generally do not itch or hurt. After lesions resolve, the affected areas may be lighter or darker than normal. If the scalp is involved, alopecia areata often occurs.

Condyloma lata are hypertrophic, flattened, dull pink or gray papules at mucocutaneous junctions and in moist areas of the skin (eg, in the perianal area, under the breasts); lesions are extremely infectious. Lesions of the mouth, throat, larynx, penis, vulva, or rectum are usually circular, raised, and often gray to white with a red border.

Secondary syphilis can affect any organ. About half of patients have lymphadenopathy, usually generalized, with nontender, firm, discrete nodes, and often hepatosplenomegaly. About 10% of patients have lesions of the eyes (uveitis), bones (periostitis), joints, meninges, kidneys (glomerulitis), liver

(hepatitis), or spleen. About 10 to 30% of patients have mild meningitis, but < 1% have meningeal symptoms, which can include headache, neck stiffness, cranial nerve lesions, deafness, and eye inflammation (eg, optic neuritis, retinitis).

Latent period: Symptoms and signs are absent, but antibodies, detected by serologic tests for syphilis (STS), persist. Because symptoms of primary and secondary syphilis are often minimal or ignored, patients frequently are first diagnosed during the latent stage when routine blood tests for syphilis are done. Syphilis may remain latent permanently, but relapses with contagious skin or mucosal lesions may occur during the early latent period (< 1 yr after infection). Patients are often given antibiotics for other disorders, which may cure latent syphilis and may account for the rarity of late-stage disease in developed countries.

Late or tertiary syphilis: About one third of untreated people develop late syphilis, although not until years to decades after the initial infection. Lesions may be clinically classified as benign tertiary syphilis, cardiovascular syphilis, or neurosyphilis.

Benign tertiary gummatous syphilis usually develops within 3 to 10 yr of infection and may involve the skin, bones, and internal organs. Gummas are soft, destructive, inflammatory masses that are typically localized but may diffusely infiltrate an organ or tissue; they grow and heal slowly and leave scars.

Benign tertiary syphilis of bone results in either inflammation or destructive lesions that cause a deep, boring pain, characteristically worse at night.

Cardiovascular syphilis usually manifests 10 to 25 yr after the initial infection as aneurysmal dilation of the ascending aorta, insufficiency of the aortic valve, or narrowing of the coronary arteries. Pulsations of the dilated aorta may cause symptoms by compressing or eroding adjacent structures in the chest. Symptoms include brassy cough, infections, and obstruction of breathing due to pressure on the trachea, hoarseness due to vocal cord paralysis resulting from compression of the left laryngeal nerve, and painful erosion of the sternum and ribs or spine.

Neurosyphilis has several forms:

• Asymptomatic neurosyphilis

• Meningovascular neurosyphilis

• Parenchymatous neurosyphilis

• Tabes dorsalis

Asymptomatic neurosyphilis causes mild meningitis in about 15% of patients originally diagnosed as having latent syphilis, in 25 to 40% of those with secondary syphilis, in 12% of those with cardiovascular syphilis, and in 5% of those with benign tertiary syphilis. Without treatment, it evolves to symptomatic neurosyphilis in 5%. If CSF examination does not detect evidence of meningitis 2 yr after the initial infection, neurosyphilis is unlikely to develop.

Meningovascular neurosyphilis results from inflammation of large- to medium-sized arteries of the brain or spinal cord; symptoms typically occur 5 to 10 yr after infection and range from none to strokes. Initial symptoms may include headache, neck stiffness, dizziness, behavioral abnormalities, poor concentration, memory loss, lassitude, insomnia, and blurred vision. Spinal cord involvement may cause weakness and wasting of shoulder-girdle and arm muscles, slowly progressive leg weakness with urinary or fecal incontinence or both, and, rarely, sudden paralysis of the legs due to thrombosis of spinal arteries.

Parenchymatous neurosyphilis (general paresis, or dementia paralytica) results when chronic meningoencephalitis causes destruction of cortical parenchyma. It usually develops 15 to 20 yr after initial infection and typically does not affect patients before their 40s or 50s. Behavior progressively deteriorates, sometimes mimicking a mental disorder or dementia. Irritability, difficulty concentrating,

deterioration of memory, defective judgment, headaches, insomnia, fatigue, and lethargy are common; seizures, aphasia, and transient hemiparesis are possible. Hygiene and grooming deteriorate. Patients may become emotionally unstable and depressed and have delusions of grandeur with lack of insight; wasting may occur. Tremors of the mouth, tongue, outstretched hands, and whole body may occur; other signs include pupillary abnormalities, dysarthria, hyperreflexia, and, in some patients, extensor plantar responses. Handwriting is usually shaky and illegible.

Tabes dorsalis (locomotor ataxia) involves slow, progressive degeneration of the posterior columns and nerve roots. It typically develops 20 to 30 yr after initial infection; mechanism is unknown. Usually, the earliest, most characteristic symptom is an intense, stabbing (lightning) pain in the back and legs that recurs irregularly. Gait ataxia, hyperesthesia, and paresthesia may produce a sensation of walking on foam rubber. Loss of bladder sensation leads to urine retention, incontinence, and recurrent infections. Erectile dysfunction is common.

Most patients with tabes dorsalis are thin and have characteristic sad facies and Argyll Robertson pupils (pupils that accommodate for near vision but do not respond to light). Optic atrophy may occur. Examination of the legs detects hypotonia, hyporeflexia, impaired vibratory and joint position sense, ataxia in the heel-shin test, absence of deep pain sensation, and Romberg's sign. Tabes dorsalis tends to be intractable even with treatment. Visceral crises (episodic pain) are a variant of tabes dorsalis; paroxysms of pain occur in various organs, most commonly in the stomach (causing vomiting) but also in the rectum, bladder, and larynx.

Other lesions: Syphilitic ocular and otic manifestations can occur at any stage of the disease. Ocular syndromes can affect virtually any part of the eye; they include interstitial keratitis, uveitis (anterior, intermediate, and posterior), chorioretinitis, retinitis, retinal vasculitis, and cranial nerve and optic neuropathies. Otosyphilis may affect the cochlea (causing hearing loss and tinnitus) or vestibular system (causing vertigo and nystagmus).

Trophic lesions, secondary to hypoesthesia of the skin or periarticular tissues, may develop in the later stages. Trophic ulcers may develop on the soles of the feet and penetrate as deeply as the underlying bone. Neurogenic arthropathy (Charcot's joints), a painless joint degeneration with bony swelling and abnormal range of movement, is a classic manifestation of neuropathy (see p.).

Diagnosis

• Serologic reaginic tests (rapid plasma reagin, Venereal Disease Research Laboratory) for screening

• Serologic treponemal tests (eg, fluorescent treponemal antibody absorption) for confirmation

Syphilis should be suspected in patients with typical mucocutaneous lesions or unexplained neurologic disorders, particularly in areas where the infection is prevalent. In such areas, it should also be considered in patients with a broad range of unexplained findings. Because clinical manifestations are so diverse and advanced stages are now relatively rare in most developed countries, syphilis may escape recognition. Patients with HIV and syphilis may have atypical or accelerated disease.

Diagnostic test selection depends on which stage of syphilis is suspected. Cases must be reported to public health agencies.

Diagnostic tests for syphilis: Tests include serologic tests for syphilis (STS), which consist of screening (reaginic) and confirmatory (treponemal) tests, and darkfield microscopy. *T. pallidum* cannot be grown in vitro.

Reaginic tests use lipid antigens (cardiolipin from bovine hearts) to detect reagin (human antibodies that bind to lipids). The Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests are sensitive, simple, and inexpensive reaginic tests that are used for screening but are not specific for syphilis. Results may be presented qualitatively (eg, reactive, weakly reactive, borderline, or nonreactive) and quantitatively as titers (eg, positive at 1:16 dilution).

Many disorders other than treponemal infections (eg, SLE, antiphospholipid antibody syndromes) can produce a positive (biologically false-positive) reagin test result. CSF reaginic tests are reasonably sensitive for early disease but less so for late neurosyphilis. CSF reagin tests can be used to diagnose neurosyphilis or to monitor response to treatment by measuring antibody titers.

Treponemal tests detect antitreponemal antibodies qualitatively and are very specific for syphilis. They include the following:

• Fluorescent treponemal antibody absorption (FTA-ABS) test

• Microhemagglutination assay for antibodies to *T. pallidum* (MHA-TP)

• *T. pallidum* hemagglutination assay (TPHA)

If they do not confirm treponemal infection after a positive reaginic test, the reaginic result is biologically false-positive. Treponemal tests of CSF are controversial, but some authorities believe the FTA-ABS test is sensitive.

Neither reaginic nor treponemal tests become positive until 3 to 6 wk after the initial infection. Thus, a negative result is common in early primary syphilis and does not exclude syphilis until after 6 wk. Reaginic titers decline after effective treatment, becoming negative by 1 yr in primary and by 2 yr in secondary syphilis. Treponemal tests usually remain positive for many decades, despite effective treatment.

Darkfield microscopy directs light obliquely through a slide of exudate from a chancre or lymph node aspirate to directly visualize spirochetes. Although the skills and equipment required are not usually available, darkfield microscopy is the most sensitive and specific test for early primary syphilis. The spirochetes appear against a dark background as bright, motile, narrow coils that are about 0.25 μm wide and 5 to 20 μm long. They must be distinguished morphologically from nonpathogenic spirochetes, which may be part of the normal flora, especially of the mouth.

Primary syphilis: Primary syphilis is usually suspected based on relatively painless genital (but occasionally extragenital) ulcers. Syphilitic ulcers should be differentiated from other sexually transmitted genital lesions (see Table 156-1). Co-infections with 2 ulcer-causing pathogens (eg, herpes simplex virus plus *T. pallidum*) are not rare.

Darkfield microscopy of exudate from a chancre or lymph node aspirate may be diagnostic. If results are negative or the test is unavailable, a reaginic STS is done. If results are negative or the test cannot be done immediately but a skin lesion has been present for < 3 wk (before the STS becomes positive) and an alternate diagnosis seems unlikely, treatment may be instituted, and the STS repeated in 2 to 4 wk. Patients with syphilis should be tested for other sexually transmitted diseases (STDs), including HIV, at diagnosis and 6 mo later.

Secondary syphilis: Because syphilis can mimic many diseases, it should be considered when any cutaneous eruption or mucosal lesion is undiagnosed, particularly if patients have any of the following:

• Generalized lymphadenopathy

• Lesions on the palms or soles

• Condyloma lata

• Risk factors (eg, HIV, multiple sex partners)

Clinically, secondary syphilis may be mistaken for a drug eruption, rubella, infectious mononucleosis, erythema multiforme, pityriasis rubra pilaris, fungal infection, or, particularly, pityriasis rosea. Condyloma lata may be mistaken for warts, hemorrhoids, or pemphigus vegetans; scalp lesions may be mistaken for ringworm or idiopathic alopecia areata.

Secondary syphilis is excluded by a negative reaginic STS, which is virtually always reactive during this stage, often with a high titer. A compatible syndrome with a positive STS (reaginic or treponemal) warrants treatment. Uncommonly, this combination represents latent syphilis coexisting with another skin disease. Patients with secondary syphilis should be tested for other STDs and for asymptomatic neurosyphilis.

Latent syphilis: Asymptomatic, latent syphilis is diagnosed when reaginic and treponemal STSs are positive in the absence of symptoms or signs of active syphilis. Such patients should have a thorough examination, particularly genital, skin, neurologic, and cardiovascular examinations, to exclude secondary and tertiary syphilis. Treatment and serologic follow-up for up to several years may be needed to ensure the success of therapy because reaginic STS titers decrease slowly.

Latent acquired syphilis must be differentiated from latent congenital syphilis (see p.), latent yaws, and other treponemal infections.

Late or tertiary syphilis: Patients with symptoms or signs of tertiary syphilis (particularly unexplained neurologic abnormalities) require STS. If the test is reactive, the following should be done:

• Lumbar puncture for CSF examination (including STS)

• Imaging of the brain and aorta

• Screening of any other organ systems clinically suspected to be involved

At this stage of syphilis, a reaginic STS is nearly always positive, except in a few cases of tabes dorsalis.

In benign tertiary syphilis, differentiation from other inflammatory mass lesions or ulcers may be difficult without biopsy.

Cardiovascular syphilis is suggested by symptoms and signs of aneurysmal compression of adjacent structures, particularly stridor or hoarseness.

Syphilitic aortic aneurysm is suggested by aortic insufficiency without aortic stenosis and, on chest x-ray, by widening of the aortic root and linear calcification on the walls of the ascending aorta. Diagnosis of aneurysm is confirmed with aortic imaging (transesophageal echocardiography, CT, or MRI).

In neurosyphilis, most symptoms and signs, except for Argyll Robertson pupil, are non-specific, so that diagnosis relies heavily on a high index of clinical suspicion. Asymptomatic neurosyphilis is diagnosed based on abnormal CSF (typically, lymphocytic pleocytosis and elevated protein) and a reactive CSF reaginic test. In parenchymatous neurosyphilis, the CSF reaginic and serum treponemal tests are reactive and CSF typically has lymphocytic pleocytosis and elevated protein. If present, HIV may confound the diagnosis because it causes mild pleocytosis and various other neurologic symptoms.

In tabes dorsalis, serum reaginic tests may be negative if patients have been previously treated, but serum treponemal tests are usually positive. CSF usually has lymphocytic pleocytosis and elevated protein, and sometimes reaginic or treponemal test results are positive; however, in many treated patients, CSF is normal.

Treatment

• Sustained-release penicillin

• Treatment of sex partners

The treatment of choice in all stages of syphilis and during pregnancy is sustained-release penicillin (ie, benzathine penicillin). All sex partners within the past 3 mo (if primary syphilis is diagnosed) and within 1 yr (if secondary syphilis is diagnosed) should be evaluated and, if infected, treated.

Primary, secondary, and latent syphilis: Benzathine penicillin G 2.4 million units IM given once produces blood levels that are sufficiently high for 2 wk to cure primary, secondary, and early (< 1 yr) latent syphilis. Doses of 1.2 million units are usually given in each buttock to reduce local reactions. Additional injections of 2.4 million units should be given 7 and 14 days later for late (> 1 yr) latent syphilis or latent syphilis of unknown duration because treponemes occasionally persist in the CSF after single-dose regimens.

Patients with a history of IgE (anaphylactic or urticarial) allergic reactions to penicillin should not be treated with a cephalosporin because they may have an allergic reaction. Azithromycin 2 g po in a single dose or doxycycline 100 mg po bid for 14 days may be used, but efficacy of these drugs is not well-defined, particularly for late latent syphilis, and the 14-day regimen requires good adherence. If adherence to the 14-day regimen cannot be ensured, the risk of using a cephalosporin may be justifiable. Ceftriaxone 125 mg IM or IV once/day for 10 days has been effective in a limited number of patients.

Late or tertiary syphilis: Benign or cardiovascular tertiary syphilis can be treated in the same way as late latent syphilis.

For ocular syphilis or neurosyphilis, aqueous penicillin 3 to 4 million units IV q 4 h for 10 days (best penetrates the CNS but may be impractical) or procaine penicillin G 2.4 million units IM once/day plus 500 mg probenecid po qid is recommended; both drugs are given for 10 to 14 days, followed by benzathine penicillin 2.4 million units once/wk for 3 wk. For patients who have penicillin allergies, azithromycin and doxycycline are effective, so penicillin desensitization is usually not indicated. Ceftriaxone 2 g IM or IV once/day for 14 days can also be effective, but cross-sensitivity with cephalosporins is a concern so it is usually avoided.

Treatment of asymptomatic neurosyphilis appears to prevent the development of new neurologic deficits. Patients with neurosyphilis may be given oral or IM antipsychotics to help control paresis. Patients with tabes dorsalis and lightning pains should be given analgesics as needed; carbamazepine 200 mg po tid or qid sometimes helps.

Jarisch-Herxheimer reaction (JHR): Most patients with primary or secondary syphilis, especially those with secondary syphilis, have a JHR within 6 to 12 h of initial treatment. It typically manifests as malaise, fever, headache, sweating, rigors, anxiety, or a temporary exacerbation of the syphilitic lesions. The mechanism is not understood, and JHR may be misdiagnosed as an allergic reaction. JHR usually subsides within 24 h and poses no danger. However, patients with general paresis or a high CSF cell count may have a more serious reaction, including seizures or strokes, and should be warned and observed accordingly. Unanticipated JHR may occur if patients with undiagnosed syphilis are given antitreponemal antibiotics for other infections.

Posttreatment surveillance: After treatment, patients should have

• Examinations and reaginic tests at 3, 6, and 12 mo and annually thereafter until the test is nonreactive

• For neurosyphilis, CSF testing every 6 mo until CSF cell count is normal

The importance of repeated tests to confirm cure should be explained to patients before treatment. Examinations and reaginic tests should be done at 3, 6, and 12 mo after treatment and annually thereafter until the test is nonreactive. Failure of titers to decline by 4-fold at 6 mo suggests treatment failure and indicates the need for retreatment. After successful treatment, primary lesions heal rapidly, and plasma reaginic titers fall and usually become qualitatively negative within 9 to 12 mo. In about 15% of patients with primary or secondary syphilis treated as recommended, the reaginic titer does not decrease by 4-fold —the criterion used to define response at 1 yr after treatment. Treponemal tests may remain positive for decades or permanently and should not be measured to monitor progress. Serologic or clinical relapse, usually affecting the nervous system, may occur after 6 to 9 mo, but the cause may be reinfection rather than relapse.

Patients with neurosyphilis require CSF testing at 6-mo intervals until the CSF cell count is normal. In HIV-infected patients, persisting CSF pleocytosis may represent effects of HIV rather than persisting

neurosyphilis. Normal CSF, serologic test, and examination results for 2 yr indicates probable cure. If the CSF WBC count remains abnormal 2 yr after maximal treatment, it is unclear whether treatment should be continued. Indications for retreatment with a more intensive regimen of antibiotics include a reaginic test that remains reactive for > 2 yr, an increasing titer, and clinical relapse.

Trichomoniasis

Trichomoniasis is infection of the vagina or male genital tract with *Trichomonas vaginalis*. It can be asymptomatic or cause urethritis, vaginitis, or occasionally cystitis, epididymitis, or prostatitis. Diagnosis is by microscopic examination of vaginal or prostatic secretions or by urethral culture. Patients and sex partners are treated with metronidazole.

T. vaginalis is a flagellated, sexually transmitted protozoan that more often infects women (about 20% of women of reproductive age) than men. Infection may be asymptomatic in either sex, but asymptomatic is the rule for men. In men, protozoa may persist for long periods in the GU tract without causing symptoms; thus, protozoa may be transmitted unwittingly to sex partners. Trichomoniasis may account for up to 5% of nongonococcal, nonchlamydial urethritis in men in some areas. Coinfection with gonorrhea and other sexually transmitted diseases (STDs) is common.

Symptoms and Signs

In women, symptoms range from none to copious, yellow-green, frothy vaginal discharge with soreness of the vulva and perineum, dyspareunia, and dysuria. Asymptomatic infection may become symptomatic at any time as the vulva and perineum become inflamed and edema develops in the labia. The vaginal walls and surface of the cervix may have punctate, red "strawberry" spots. Urethritis and possibly cystitis may also occur.

Men are usually asymptomatic; however, sometimes urethritis results in a discharge that may be transient, frothy, or purulent or that causes dysuria and frequency, usually early in the morning. Often, urethritis is mild and causes only minimal urethral irritation and occasional moisture at the urethral meatus, under the foreskin, or both. Epididymitis and prostatitis are rare complications.

Diagnosis

• Microscopic examination of vaginal secretions

• Culture of male urine or urethral swab

Trichomoniasis is suspected in women with vaginitis, in men with urethritis, and in their sex partners. Suspicion is high if symptoms persist after patients have been evaluated and treated for other infections such as gonorrhea and chlamydial, mycoplasmal, and ureaplasmal infections.

In women, diagnosis is based on clinical criteria and in-office testing. Vaginal secretions are obtained from the posterior fornix. The pH is measured. Secretions are then placed on 2 slides; they are diluted with 10% K hydroxide on one slide (KOH wet mount) and with 0.9% NaCl on the other (saline wet mount). For the whiff test, the KOH wet mount is checked for a fishy odor, which results from amines produced in trichomonas vaginitis or bacterial vaginosis. The saline wet mount is examined microscopically as soon as possible to detect trichomonads, which can become immotile and more difficult to recognize within minutes after slide preparation. (Trichomonads are pear-shaped with flagella, often motile, and average 7 to 10 μm—about the size of WBCs—but occasionally reach 25 μm.) If trichomoniasis is present, numerous neutrophils are also present.

If results are inconclusive, cultures, which are more sensitive than microscopy, are done. Trichomoniasis is also commonly diagnosed when a Papanicolaou test is done.

In men, microscopy of urine is insensitive, although occasionally organisms are visible in a first-voided morning specimen or a centrifuged specimen. Cultures of urine and urethral swabs are more sensitive.

As with diagnosis of any STD, patients with trichomoniasis should be tested to exclude other common STDs such as gonorrhea and chlamydial infection.

Treatment

• Oral metronidazole or tinidazole

• Treatment of sex partners

Metronidazole or tinidazole 2 g po in a single dose cures up to 95% of women if sex partners are treated simultaneously. Effectiveness of single-dose regimens in men is not as clear, so treatment is typically with metronidazole or tinidazole 500 mg bid for 5 to 7 days. IV metronidazole cures some women when repeated oral doses are ineffective.

Metronidazole may cause leukopenia, disulfiram-like reactions to alcohol, or candidal superinfections. It is relatively contraindicated during early pregnancy, although it may not be dangerous to the fetus after the 1st trimester. Tinidazole has not been established as safe during pregnancy and so is not used.

Sex partners should be screened and treated for trichomoniasis and other STDs. If poor adherence to follow-up is likely, treatment can be initiated in sex partners of patients with documented trichomoniasis without confirming the diagnosis in the partner.