particularly at aerobic gram-negative bacilli and anaerobes (see below) as well as etiologic studies. Secondary peritonitis usually requires both surgical intervention to address the inciting process and antibiotic administration to treat early bacteremia, to decrease the incidence of abscess formation and wound infection, and to prevent more distant spread of infection. InSBP in adults, surgery is rarely indicated. In secondary peritonitis, surgery may be life-saving.

## PERITONITIS IN PATIENTS UNDERGOING CAPD

A third type of peritonitis arises in patients who are undergoing continuous ambulatory peritoneal dialysis (CAPD). Unlike primary and secondary peritonitis, which are caused by endogenous bacteria, peritonitis in CAPD patients usually involves skin organisms. The pathogenesis of infection is similar to that of intravascular-device infection, in which skin organisms migrate along the catheter, which both serves as an entry point and exerts the effects of a foreign body. Exit-site or tunnel infection may or may not accompany CAPD peritonitis. Like primary peritonitis, CAPD peritonitis is usually caused by a single organism. Peritonitis is, in fact, the most common reason for discontinuation of CAPD. Improvements in equipment design, especially that of the Y-set connector, have resulted in a decrease from one case of peritonitis per 9 months of CAPD to one case per 15 months.

The clinical presentation ofCAPDperitonitis resembles that of secondary peritonitis in that diffuse pain and peritoneal signs are common. The dialysate is usually cloudy and contains>100WBCs per microliter, >50% of which are neutrophils. The most common etiologic organism is coagulase-negative *Staphylococcus*, which accounts for ~30% of cases. *S. aureus* causes ~10% of cases, is more commonly identified among patients who are nasal carriers of the organism, and is the most frequent pathogen in those with an overt exit-site infection. Gram-negative bacilli and fungi such as *Candida* species are also found. Vancomycin-resistant enterococci (VRE) and vancomycin-intermediate *S. aureus* (VISA) have been reported to produce peritonitis in CAPD patients. The finding of more than one organism in dialysate culture should prompt a search for a cause of secondary peritonitis. As with primary peritonitis, culture of dialysate fluid in blood culture bottles improves the yield.

## TREATMENT

Empirical therapy forCAPDperitonitis should be directed at coagulase-negative *Staphylococcus*, *S. aureus*, and gram-negative bacilli until the results of cultures are available. Since the advent ofVRE andVISA, recommended treatment has changed from vancomycin and an aminoglycoside to a first-generation cephalosporin such as cefazolin and an aminoglycoside, which can be administered together in the same bag. A loading dose of cefazolin (500 mg/L) is administered intraperitoneally, with a maintenance dose of 125 mg/L in each bag. Ototoxicity is a significant concern in patients receiving aminoglycosides; some data suggest that administration of a single daily dose lessens this risk. Thus, gentamicin is usually administered at a dose of 20 mg/L once a day. If methicillin-resistant *S. aureus* is a relatively common isolate in a community, vancomycin may still be a reasonable first choice for empirical therapy, especially in a toxic-appearing patient or a patient with an overt exit-site infection. The dose (2 g) is allowed to remain in the peritoneal cavity for 6 h. The clinical response to

an empirical treatment regimen should be rapid; if the patient has not responded after 48 h of treatment, catheter removal should be considered.

## INTRAPERITONEAL ABSCESSES

Abscess formation is common in untreated peritonitis if overt gram-negative sepsis either does not develop or develops but is not fatal. In experimental models of abscess formation, mixed aerobic and anaerobic organisms have been implanted intraperitoneally. Without therapy directed at anaerobes, animals develop intraabdominal abscesses. As in humans, these experimental abscesses may stud the peritoneal cavity, lie within the omentum or mesentery, or even develop on the surface of or within viscera such as the liver.

### PATHOGENESIS AND IMMUNITY

There is often disagreement about whether an abscess represents a disease state or a host response. In a sense, it represents both: While an abscess is an infection in which viable infecting organisms andPMNs are contained in a fibrous capsule, it is also a process by which the host confines microbes to a limited space, thereby preventing further spread of infection. Experimental work has helped to define both the host cells and the bacterial virulence factors responsible -- most notably, in the case of *B. fragilis*. This organism, although accounting for only 0.5% of the normal colonic flora, is the anaerobe most frequently isolated from intraabdominal infections and is the most common anaerobic bloodstream isolate. On clinical grounds, therefore, *B. fragilis* appears to be uniquely virulent. Moreover, *B. fragilis* causes abscesses in animal models of intraabdominal infection, whereas most other *Bacteroides* species must act synergistically with a facultative organism to induce abscess formation.

Of the several virulence factors identified in *B. fragilis*, one is critical -- the capsular polysaccharide complex (CPC) found on the bacterial surface. The CPC comprises several distinct surface polysaccharides. Structural analysis of the polysaccharides in the CPC has shown an unusual motif of oppositely charged sugars. Polysaccharides having these *zwitterionic* characteristics evoke a host response in the peritoneal cavity that localizes bacteria into abscesses. *B. fragilis* and the CPC have been found to adhere to primary mesothelial cells in vitro; this adherence, in turn, stimulates the production of tumor necrosis factora (TNF-a) and intercellular adhesion molecule 1 (ICAM-1) by peritoneal macrophages. Mice treated with antibodies to TNF-a or ICAM-1 did not develop abscesses in the mouse peritonitis model. Although abscesses characteristically containPMNs, the process of abscess induction depends on the stimulation of T lymphocytes by these unique polysaccharides. Experimentally, the essential role of T cells in initiating abscess formation has been proven following blockage of the CD28-B7 costimulatory pathway. The alternative pathways of complement and fibrinogen also participate in abscess formation.

While antibodies to theCPC are not critical in immunity to abscesses, they enhance bloodstream clearance of *B. fragilis*. When administered subcutaneously, *B. fragilis* surface polysaccharide A (PS A) has immunomodulatory characteristics and stimulates T cells via an interleukin-2-dependent mechanism to inhibit the host response of abscess formation to intraperitoneal challenge with *B. fragilis*. Treatment of

experimental animals with PS A or other zwitterionic molecules reduces abscess development and can be administered after bacterial contamination of the peritoneal cavity.

## CLINICAL PRESENTATION

Most intraperitoneal abscesses result from fecal spillage from a colonic source, such as an inflamed appendix. Of all intraabdominal abscesses, 74% are intraperitoneal or retroperitoneal and are not visceral. Abscesses can also arise from a number of other processes. They usually form within weeks of the development of peritonitis and may be found in a variety of locations, from omentum to mesentery, pelvis to psoas muscles, and subphrenic space to a visceral organ such as the liver, where they may develop either on the surface of the organ or within it. Periappendiceal and diverticular abscesses have traditionally been frequent. Diverticular abscesses are least likely to rupture. Infections of the female genital tract and pancreatitis are also among the more common causative events. When abscesses occur in the female genital tract -- either as a primary infection (e.g., tuboovarian abscess) or as an infection extending into the pelvic cavity or peritoneum -- *B. fragilis* figures prominently among the organisms isolated. *B. fragilis* is not found in large numbers in the normal vaginal flora. It is encountered less commonly in pelvic inflammatory disease and endometritis, for example, without an associated abscess. In pancreatitis with leakage of damaging pancreatic enzymes, inflammation is prominent. Therefore, clinical findings such as fever, leukocytosis, and even abdominal pain do not distinguish pancreatitis itself from complications such as pancreatic pseudocyst, pancreatic abscess (Chap. 304), or intraabdominal collections of pus. Especially in cases of necrotizing pancreatitis, in which the incidence of local pancreatic infection may be as high as 30%, needle aspiration underCTguidance is performed as often as once a week to sample fluid for culture. Many centers prescribe prophylactic antibiotics to prevent infection in patients with necrotizing pancreatitis. Imipenem is the most frequently used drug for this purpose since it achieves high tissue levels in the pancreas, although it is not unique in this regard. If infected fluid is removed during needle aspiration, most experts agree that surgery is superior to percutaneous drainage.

The psoas muscle of the anterior back is another location in which abscesses are encountered. These abscesses may arise from a presumed hematogenous source, by contiguous spread from an intraabdominal or pelvic process, or by contiguous spread from nearby bony structures such as vertebral bodies. Associated osteomyelitis due to spread from bone to muscle or from muscle to bone is common in psoas abscesses. When Pott's disease was common, *Mycobacterium tuberculosis* was a frequent cause of psoas abscess. Currently in the United States, the usual isolates from psoas abscesses are either *S. aureus* or a mixture of enteric organisms including aerobic gram-negative bacilli. *S. aureus* is most likely to be isolated when a psoas abscess arises from hematogenous spread or a contiguous focus of osteomyelitis; a mixed enteric flora is most likely when the abscess has an intraabdominal or pelvic source.

## DIAGNOSIS

A variety of scanning procedures have considerably facilitated the diagnosis of intraabdominal abscesses. AbdominalCTprobably has the highest yield, although

ultrasonography is particularly useful for the right upper quadrant, kidneys, and pelvis. Both indium-labeledWBCs and gallium tend to localize in abscesses and may be useful in finding a collection. Since gallium is taken up in the bowel, indium-labeled WBCs may have a slightly greater yield for abscesses near the bowel. Neither indium-labeled WBC nor gallium scans serve as a basis for a definitive diagnosis, however; both need to be followed by other, more specific studies, such as CT, if an area of possible abnormality is identified. Abscesses contiguous with or contained within outpouchings of bowel are particularly difficult to diagnose with scanning procedures. Occasionally, a barium enema may detect a diverticular abscess not diagnosed by other procedures, although barium should not be injected if a free perforation is suspected. If one study is negative, a second study sometimes reveals a collection. On occasion, exploratory laparotomy still must be undertaken if an abscess is strongly suspected on clinical grounds, although this procedure has been less commonly used since the advent of CT.

## TREATMENT

An algorithm for the management of patients with intraabdominal abcesses is presented in Fig. 130-1. The treatment of intraabdominal infections involves the determination of the initial focus of infection, the administration of broad-spectrum antibiotics targeted at organisms involved in the associated infection, and the performance of a drainage procedure if one or more definitive abscesses have formed already. It cannot be overemphasized that antimicrobial therapy, in general, is adjunctive to drainage and/or surgical correction of an underlying lesion or process in intraabdominal abscesses (Fig. 130-CD1). Unlike the intraabdominal abscesses precipitated by most infections, for which drainage of some kind is generally required, abscesses associated with diverticulitis usually wall off locally after rupture of a diverticulum, so that surgical intervention is not routinely required.

A number of antimicrobial agents exhibit excellent activity against aerobic gram-negative bacilli. Since mortality in intraabdominal sepsis is linked to gram-negative bacteremia, empirical therapy for intraabdominal infection always needs to include adequate coverage of gram-negative aerobic and facultative organisms. Aminoglycosides and second- and third-generation cephalosporins are the agents most widely tested and used in intraabdominal processes. Newer antibiotics, such as aztreonam, imipenem, ticarcillin/clavulanic acid, piperacillin/tazobactam, and quinolones (e.g., ciprofloxacin), cover these organisms as well, although at a higher cost. Second-generation cephalosporins, such as cefoxitin or cefotetan, are not as uniformly active as the other agents against all of the aerobic gram-negative species. Aztreonam, ciprofloxacin, aminoglycosides, and most of the third-generation cephalosporins are not active against anaerobes; for the treatment of intraabdominal infections, these drugs need to be used in combination with another antibiotic. Since a number of antibiotics highly effective against anaerobes are available, third-generation cephalosporins generally should not be considered for use against the anaerobic bacteria involved in intraabdominal sepsis.

The most active and cost-effective antibiotic for anaerobic coverage currently is metronidazole (Chap. 167). Only rare isolates of *B. fragilis* have been reported to be resistant to this drug. In a study of 3177 anaerobic isolates from eight centers in the United States over a 5-year period, no strains resistant to metronidazole were

documented among *B. fragilis* isolates, and resistance to imipenem, ampicillin/sulbactam, and piperacillin/tazobactam was exceedingly rare. In contrast, resistance to cefotetan, ceftizoxime, and clindamycin increased during this interval, and resistance to cefoxitin was measurable but unchanged during the study. Despite increasing reports of in vitro resistance of *B. fragilis* to a number of agents, clinical failures are still limited to case reports; therefore, the clinical significance of antimicrobial resistance in anaerobes is uncertain. One report describes a bloodstream isolate of *B. fragilis* with resistance to metronidazole and with reduced susceptibility to imipenem and amoxicillin/clavulanic acid that became resistant to both of the latter two drugs after treatment of the patient with imipenem. Among newer agents, imipenem, ticarcillin/clavulanic acid, piperacillin/tazobactam, meropenem, and ampicillin/sulbactam are highly active against anaerobes. Chloramphenicol, which exhibits strong activity against *B. fragilis* in vitro, nevertheless should probably not be considered a first-line drug for use against anaerobes, since failures of treatment have been documented in both experimental and clinical intraabdominal infections. Neither metronidazole nor clindamycin covers aerobic gram-negative bacilli; thus, these drugs must be combined with other agents for use in this setting. Metronidazole is also less active against gram-positive than against gram-negative anaerobic species.

## VISCERAL ABSCESSES

**Liver Abscesses** The liver is the organ most subject to the development of abscesses. Altemeier and associates studied 540 intraabdominal abscesses over a 12-year period. Of these abscesses 26% were visceral. Liver abscesses made up 13% of the total number of abscesses, or 48% of all visceral abscesses. Liver abscesses may be solitary or multiple (Fig. 130-CD2); they may arise from hematogenous spread of bacteria or from local spread from contiguous sites of infection within the peritoneal cavity. In the past, appendicitis with rupture and subsequent spread of infection was the most common route for the development of a liver abscess. Currently, associated disease of the biliary tract is most often the etiology. Suppurative pylephlebitis (suppurative thrombosis of the portal vein), usually arising from infection in the pelvis but sometimes from infection elsewhere in the peritoneal cavity, is another common source for bacterial seeding of the liver.

Fever is the most common presenting sign of liver abscess. Some patients, particularly those with active associated disease of the biliary tract, have symptoms and signs localized to the right upper quadrant, including pain, guarding, punch tenderness, and even rebound tenderness. Nonspecific symptoms, such as chills, anorexia, weight loss, nausea, and vomiting, may also develop. Only 50% of patients with liver abscesses, however, have hepatomegaly, right-upper-quadrant tenderness, or jaundice; thus, half of patients have no symptoms or signs that would direct attention to the liver. Fever of unknown origin (FUO) may be the only presenting manifestation of liver abscess, especially in the elderly. Diagnostic studies of the abdomen, especially the right upper quadrant, should be a part of any FUO workup. The single most reliable laboratory finding is an elevated serum concentration of alkaline phosphatase, which is documented in 70% of patients with liver abscesses. Other tests of liver function may yield normal results, but 50% of patients have elevated serum levels of bilirubin, and 48% have elevated concentrations of aspartate aminotransferase. Other associated laboratory findings include leukocytosis in 77% of patients, anemia (usually

normochromic, normocytic) in 50%, and hypoalbuminemia in 33%. Concomitant bacteremia is found in one-third of patients. A liver abscess is sometimes suggested by chest radiography, especially if a new elevation of the right hemidiaphragm is seen; other suggestive findings include a right basilar infiltrate and a right pleural effusion.

Imaging studies are the most reliable methods for diagnosing liver abscesses. These studies include ultrasonography,CT, indium-labeledWBC or gallium scans, and even magnetic resonance imaging. In an occasional case, more than one such study may be required. Organisms recovered from liver abscesses vary with the etiology. In liver infection arising from the biliary tree, enteric gram-negative aerobic bacilli and enterococci are common isolates. Unless previous surgery has been performed, anaerobes are not generally involved in liver abscesses arising from biliary infections. In contrast, in liver abscesses arising from pelvic and other intraperitoneal sources, a mixed flora including aerobic and anaerobic species (especially *B. fragilis*) is common. With hematogenous spread of infection, usually only a single organism is encountered; this species may be *S. aureus* or a streptococcal species such as *S. milleri.*

Liver abscesses may also be caused by *Candida* species; such abscesses usually follow fungemia in patients receiving chemotherapy for cancer and often present when neutrophils return after a period of neutropenia. Amebic liver abscesses are not an uncommon problem (Chap. 213). Amebic serologic testing gives positive results in >95% of cases; thus, a negative result helps to exclude this diagnosis.

**TREATMENT**

While drainage -- either percutaneous (with a pigtail catheter kept in place) or surgical -- remains the mainstay of therapy for intraabdominal abscesses (including liver abscesses), there is growing interest in medical management alone for pyogenic liver abscesses. The drugs used in empirical broad-spectrum antibiotic therapy include the same ones used in intraabdominal sepsis. Usually, a diagnostic aspirate of abscess contents should be obtained before the initiation of empirical therapy, with antibiotic choices adjusted when the results of Gram's staining and culture become available. Cases treated without definitive drainage generally require longer courses of antibiotic therapy. When percutaneous drainage was compared with open surgical drainage, the average length of hospital stay for the former was almost twice that for the latter, although both the time required for fever to resolve and mortality were the same for the two procedures. Mortality was appreciable despite treatment, averaging 15%. Several factors may predict the failure of percutaneous drainage and therefore may favor primary surgical intervention. These factors include the presence of multiple, sizable abscesses; viscous abscess contents that tend to plug the catheter; associated disease (e.g., disease of the biliary tract) that requires surgery; or the lack of a clinical response to percutaneous drainage in 4 to 7 days.

Treatment of candidal liver abscesses usually entails lengthy administration of amphotericin B, although reports have described successful maintenance therapy with fluconazole after an initial course of amphotericin (Chap. 205).

**Splenic Abscesses** Splenic abscesses are much less common than liver abscesses. In fact, no splenic abscesses were observed in Altemeier's series of 540 intraabdominal

abscesses. The incidence of splenic abscesses has ranged from 0.14 to 0.7% in various autopsy series. The clinical setting and the organisms isolated usually differ from those for liver abscesses. The degree of clinical suspicion for splenic abscess needs to be high, as this condition is frequently fatal if left untreated. Even in the most recently published series, diagnosis was made only at autopsy in 37% of cases. While splenic abscesses may arise occasionally from contiguous spread of infection or from direct trauma to the spleen, hematogenous spread of infection is the usual mode of development. Bacterial endocarditis is the most common associated infection. Splenic abscesses can develop in patients who have received extensive immunosuppressive therapy (particularly those with malignancy involving the spleen) and in patients with hemoglobinopathies or other hematologic disorders (especially sickle cell anemia).

While ~50% of patients with splenic abscesses have abdominal pain, the pain is localized to the left upper quadrant in only half of these cases. Splenomegaly is found in ~50% of cases. Fever and leukocytosis are generally present; the development of fever preceded diagnosis by an average of 20 days in one series. Left-sided chest findings may include abnormalities to auscultation, and chest radiographic findings may include an infiltrate or a left-sided pleural effusion. When splenic abscesses are being considered in a differential diagnosis,CT scan of the abdomen has been the most sensitive diagnostic tool. Ultrasonography can yield the diagnosis, but cases have been missed with this modality. Liver-spleen scan or gallium scan may also be useful. Streptococcal species are the most common bacterial isolates from splenic abscesses, and *S. aureus* is the next most common; presumably these prevalences reflect the bacterial cause of the associated endocarditis. An increase in the frequency of isolation of gram-negative aerobic organisms from splenic abscesses has been reported; these organisms often derive from a urinary tract focus, with associated bacteremia, or from another intraabdominal source. *Salmonella* species are seen fairly commonly, especially in patients with sickle cell hemoglobinopathy. Anaerobic species accounted for only 5% of isolates in the largest collected series, but the reporting of a number of "sterile abscesses" may indicate that optimal techniques for the isolation of anaerobes were not employed.

## TREATMENT

Because of the high mortality figures reported for splenic abscesses, the treatment of choice is splenectomy with adjunctive antibiotics. However, percutaneous drainage has been successful. The most important factor in successful treatment of splenic abscesses is early consideration of the diagnosis.

**Perinephric and Renal Abscesses** Perinephric and renal abscesses are not common: The former accounted for only ~0.02% of hospital admissions and the latter for ~0.2% in Altemeier's series of 540 intraabdominal abscesses. While liver abscesses generally arise from contiguous foci of infection or track from other intraabdominal sources and splenic abscesses usually arise from hematogenous spread (e.g., spread from bacterial endocarditis), perinephric and renal abscesses have a different pathogenesis. Before antibiotics became available, most renal and perinephric abscesses were hematogenous in origin, with *S. aureus* most commonly recovered. Now, in contrast,>75% of perinephric and renal abscesses arise from an initial urinary tract infection. Infection ascends from the bladder to the kidney, with pyelonephritis occurring

first. Bacteria may directly invade the renal parenchyma from medulla to cortex. Local vascular channels within the kidney may also facilitate the transport of organisms. Areas of abscess developing within the parenchyma may rupture into the perinephric space. The kidneys and adrenal glands are surrounded by a layer of perirenal fat that, in turn, is surrounded by Gerota's fascia, which extends superiorly to the diaphragm and inferiorly to the pelvic fat. When abscesses extend into the perinephric space, tracking may occur through Gerota's fascia into the psoas or transversalis muscles, into the anterior peritoneal cavity, superiorly to the subdiaphragmatic space, or inferiorly to the pelvis. Of the several risk factors that have been associated with the development of perinephric abscesses, the most important is the presence of concomitant nephrolithiasis producing local obstruction to urinary flow. Of patients with perinephric abscess, 20 to 60% have renal stones. In addition, other structural abnormalities of the urinary tract, a history of urologic surgery, trauma, and diabetes mellitus have all been identified as risk factors.

The organisms most frequently encountered in perinephric and renal abscesses are *E. coli*, *Proteus* species, and *Klebsiella* species. *E. coli*, the aerobic species most commonly found in colonic flora, seems to have unique virulence properties in the urinary tract, including factors promoting adherence to uroepithelial cells. The urease of *Proteus* species splits urea, thereby creating a more alkaline and hospitable environment for bacterial proliferation. *Proteus* species are frequently found in association with large struvite stones caused by the precipitation of magnesium ammonium sulfate in an alkaline environment. These stones serve as a nidus for recurrent urinary tract infection. While a single bacterial species is usually recovered from a perinephric or renal abscess, multiple species may also be found. If a urine culture is not contaminated with periurethral flora and is found to contain more than one organism, a perinephric abscess or renal abscess should be considered in the differential diagnosis. Urine cultures may also be polymicrobial in cases of bladder diverticulum.

*Candida* species should be considered in the etiology of renal abscesses. This fungus may spread to the kidney via the hematogenous route or by ascension from the bladder. The hallmark of the latter route of infection is ureteral obstruction with large fungal balls.

The presentation of perinephric and renal abscesses is quite nonspecific. Flank pain and abdominal pain are common. At least 50% of patients are febrile. Pain may be referred to the groin or leg, particularly with extension of infection. The diagnosis of perinephric abscess, like that of splenic abscess, is frequently delayed, and mortality in some series is appreciable, although lower than in the past. Perinephric or renal abscess should be most seriously considered when a patient presents with symptoms and signs of pyelonephritis and remains febrile after 4 or 5 days, by which time the fever should have resolved. Moreover, when a urine culture yields a polymicrobial flora, when a patient is known to have renal stone disease, or when fever and pyuria coexist with a sterile urine culture, the diagnosis of perinephric or renal abscess should be entertained.

Renal ultrasonography and abdominalCT are the most useful diagnostic modalities. If a renal abscess or perinephric abscess is diagnosed, nephrolithiasis should be excluded, especially when a high urinary pH suggests the presence of a urea-splitting organism.

**TREATMENT**

Treatment for perinephric or renal abscesses, like that for other intraabdominal abscesses, includes drainage of pus and antibiotic therapy directed at the organism(s) recovered. For perinephric abscesses, percutaneous drainage is usually successful.

**Pancreatic Abscesses***See Chap. 304.*

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 131. ACUTE INFECTIOUS DIARRHEAL DISEASES AND BACTERIAL FOOD POISONING - *Joan R. Butterton*, *Stephen B. Calderwood*

Ranging from mild annoyances during vacations to devastating dehydrating illnesses that can kill within hours, acute gastrointestinal illnesses rank second only to acute upper respiratory illnesses as the most common diseases worldwide. In children <5 years old, attack rates range from 2 to 3 illnesses per child per year in developed countries to as high as 10 to 18 illnesses per child per year in developing countries. In Asia, Africa, and Latin America, acute diarrheal illnesses are not only a leading cause of morbidity in children -- with an estimated 1 billion cases per year -- but also the major cause of mortality, being responsible for 4 to 6 million deaths per year, or a sobering total of 12,600 deaths per day. In some areas, more than 50% of childhood deaths are directly attributable to acute diarrheal illnesses. In addition, by contributing to malnutrition and thereby reducing resistance to other infectious agents, gastrointestinal illnesses may be indirect factors in a far greater burden of disease.

The wide range of clinical manifestations of acute gastrointestinal illnesses is matched by the wide variety of infectious agents involved, including viruses, bacteria, and parasitic pathogens (Table 131-1). This chapter will discuss factors that enable gastrointestinal pathogens to cause disease, will review host defense mechanisms, and will delineate an approach to the evaluation and treatment of patients presenting with acute diarrhea. Individual organisms causing acute gastrointestinal illnesses are discussed in detail in subsequent chapters.

### PATHOGENIC MECHANISMS

Enteric pathogens have developed a variety of tactics to overcome host defenses. Understanding the virulence factors employed by these organisms is important in the diagnosis and treatment of clinical disease.

**Inoculum Size** The number of microorganisms that must be ingested to cause disease varies considerably from species to species. For *Shigella*, enterohemorrhagic *Escherichia coli*, *Giardia lamblia*, or *Entamoeba*, as few as 10 to 100 bacteria or cysts can produce infection, while $10^5$ to $10^8$ *Vibrio cholerae* organisms must be ingested orally to cause disease. The infective dose of *Salmonella* varies widely, depending on the species, host, and food vehicle. The ability of organisms to overcome host defenses has important implications for transmission; *Shigella*, enterohemorrhagic *E. coli*, *Entamoeba*, and *Giardia* can spread by person-to-person contact, whereas under some circumstances *Salmonella* may have to grow in food for several hours before reaching an effective infectious dose.

**Adherence** Many organisms must adhere to the gastrointestinal mucosa as an initial step in the pathogenic process; thus, organisms that can compete with the normal bowel flora and colonize the mucosa have an important advantage in causing disease. Specific cell-surface proteins involved in attachment of bacteria to intestinal cells are important virulence determinants. *V. cholerae*, for example, adheres to the brush border of small-intestinal enterocytes via specific surface adhesins, including the toxin-coregulated pilus and other accessory colonization factors. Enterotoxigenic *E. coli* produces an adherence protein called *colonization factor antigen* that is necessary for

colonization of the upper small intestine by the organism prior to the production of enterotoxin. Enteropathogenic and enterohemorrhagic strains of *E. coli* produce virulence determinants that allow these organisms to attach to and efface the brush border of the intestinal epithelium.

**Toxin Production** The production of one or more exotoxins is important in the pathogenesis of numerous enteric organisms. Such toxins include *enterotoxins*, which cause watery diarrhea by acting directly on secretory mechanisms in the intestinal mucosa; *cytotoxins*, which cause destruction of mucosal cells and associated inflammatory diarrhea; and *neurotoxins*, which act directly on the central or peripheral nervous system. Some exotoxins act by more than one mechanism; *Shigella dysenteriae* type 1, for example, produces an exotoxin that has both enterotoxic and cytotoxic activities.

The prototypical enterotoxin is cholera toxin, a heterodimeric protein composed of one A and five B subunits. The A subunit contains the enzymatic activity of the toxin, while the B subunit pentamer binds holotoxin to the enterocyte surface receptor, the ganglioside $G_{M1}$. After the binding of holotoxin, a fragment of the A subunit is translocated across the eukaryotic cell membrane into the cytoplasm, where it catalyzes the ADP-ribosylation of a GTP-binding protein and causes persistent activation of adenylate cyclase. The end result is an increase of cyclic AMP in the intestinal mucosa, which increases $Cl^-$ secretion and decreases $Na^+$absorption, leading to loss of fluid and the production of diarrhea.

Enterotoxigenic strains of *E. coli* may produce a protein called *heat-labile enterotoxin* (LT) that is similar to cholera toxin and causes secretory diarrhea by the same mechanism. Alternatively, enterotoxigenic strains of *E. coli* may produce *heat-stable enterotoxin* (ST), one form of which causes diarrhea by activation of guanylate cyclase and elevation of intracellular cyclic GMP. Some enterotoxigenic strains produce both LT and ST.

Bacterial cytotoxins, in contrast, destroy intestinal mucosal cells and produce the syndrome of dysentery, with bloody stools containing inflammatory cells. Enteric pathogens that produce such cytotoxins include *S. dysenteriae* type 1, *Vibrio parahaemolyticus*, and *Clostridium difficile*. Shiga toxin-producing strains of *E. coli*, most commonly serotype O157:H7 in the United States, produce potent cytotoxins that are highly related to the Shiga toxin of *S. dysenteriae* type 1. Such strains of *E. coli* have been associated with outbreaks of hemorrhagic colitis and hemolytic-uremic syndrome.

Neurotoxins usually are produced by the responsible organism outside the host and therefore cause symptoms soon after ingestion. Included are the staphylococcal and *Bacillus cereus* toxins, which act on the central nervous system to produce vomiting.

**Invasion** Dysentery may result not only from the production of cytotoxins but also from bacterial invasion and destruction of intestinal mucosal cells. Infections due to *Shigella* and enteroinvasive *E. coli*, for example, are characterized by the organisms' invasion of mucosal epithelial cells, intraepithelial multiplication, and subsequent spread to adjacent cells. *Salmonella*, on the other hand, causes inflammatory diarrhea by invasion of the bowel mucosa but generally is not associated with the destruction of enterocytes or the

full clinical syndrome of dysentery. *Salmonella typhi* and *Yersinia enterocolitica* can penetrate intact intestinal mucosa, multiply intracellularly in Peyer's patches and intestinal lymph nodes, and then disseminate through the bloodstream to cause enteric fever, a syndrome characterized by fever, headache, relative bradycardia, abdominal pain, splenomegaly, and leukopenia.

## HOST DEFENSES

Given the enormous number of microorganisms ingested with every meal, the normal host must possess effective defense mechanisms to combat a constant influx of potential enteric pathogens. Studies of infections in patients with alterations in these defenses have led to a greater understanding of the variety of ways in which the normal host can protect itself against disease.

**Normal Flora** The large numbers of bacteria that normally inhabit the intestine act as an important host defense by preventing colonization by potential enteric pathogens. Persons with fewer intestinal bacteria, such as infants who have not yet developed normal enteric colonization or patients receiving antibiotics, are at significantly greater risk of developing infections with enteric pathogens. The composition of the intestinal flora is as important as the number of organisms present. More than 99% of the normal colonic flora is made up of anaerobic bacteria, and the acidic pH and volatile fatty acids produced by these organisms appear to be critical elements in resistance to colonization.

**Gastric Acid** The acidic pH of the stomach is an important barrier to enteric pathogens, and an increased frequency of infections due to *Salmonella*, *G. lamblia*, and a variety of helminths has been reported among patients who have undergone gastric surgery or are achlorhydric for some other reason. Neutralization of gastric acid with antacids or $H_2$blockers -- common among hospitalized patients -- similarly increases the risk of enteric colonization. Some microorganisms, however, can survive the extreme acidity of the gastric environment; rotavirus, for example, is highly stable to acidity.

**Intestinal Motility** Normal peristalsis is the major mechanism for clearance of bacteria from the proximal small intestine, although gastric acidity and secreted immunoglobulins also play a role in limiting the number of organisms present. When intestinal motility is impaired -- for example, by treatment with opiates or other antimotility drugs, anatomic abnormalities (diverticula, fistulas, or afferent-loop stasis following surgery), or hypomotility states (as in diabetes mellitus or scleroderma) -- the frequency of bacterial overgrowth and infection of the small bowel with enteric pathogens is much increased. Some patients in whom *Shigella* infection is treated with diphenoxylate hydrochloride with atropine (Lomotil) experience prolonged fever and shedding of organisms, while patients treated with opiates for mild *Salmonella* gastroenteritis have a higher frequency of bacteremia than those not treated with opiates.

**Immunity** Both cellular immune responses and antibody production play important roles in protecting susceptible hosts from enteric infections. The wide spectrum of viral, bacterial, parasitic, and fungal gastrointestinal infections in patients with AIDS highlights the significance of cell-mediated immunity in protecting the normal host from these pathogens. Humoral immunity is also important and consists of systemic IgG and IgM

as well as secretory IgA. Growing evidence supports the concept of a mucosal immune system for secretory IgA in which binding of bacterial antigens to the luminal surface of M cells in the distal small bowel and subsequent presentation of the antigens to subepithelial lymphoid tissue lead to the proliferation of sensitized lymphocytes. These lymphocytes circulate and populate all of the mucosal tissues of the body as IgA-secreting plasma cells.

### *Approach to the Patient*

The approach to the patient with possible infectious diarrhea or bacterial food poisoning is shown inFig. 131-1.

***History*** The answers to questions with high discriminating value can quickly narrow the range of potential causes of diarrhea and help determine whether treatment is needed. Important elements of the narrative history are detailed inFig. 131-1.

***Physical Examination*** The examination of patients for signs of dehydration provides essential information about the severity of the diarrheal illness and the need for rapid therapy. Mild dehydration is indicated by thirst, dry mouth, decreased axillary sweat, decreased urine output, and slight weight loss. Signs of moderate dehydration include an orthostatic fall in blood pressure, skin tenting, and sunken eyes (or, in infants, a sunken fontanelle). Signs of severe dehydration range from hypotension and tachycardia to confusion and frank shock.

***Diagnostic Approach*** After the severity of illness is assessed, the most important distinction that the clinician must make is between *inflammatory* and *noninflammatory* disease. Using the history and epidemiologic features of the case as guides in making this distinction, the clinician can rapidly evaluate the need for further efforts to define a specific etiology and for therapeutic intervention. Examination of a stool sample is an important supplement to the narrative history (Fig. 131-CD1). Grossly bloody or mucoid stool suggests an inflammatory process, but all stools should be examined for fecal leukocytes; the latter task is accomplished by the preparation of a thin smear of the stool on a glass slide, the addition of a drop of methylene blue, and examination of the wet mount. Causes of acute infectious diarrhea, categorized as inflammatory and noninflammatory, are listed inTable 131-1.

## EPIDEMIOLOGY

**Travel History** Of the 12 to 20 million people who travel from temperate industrialized countries to tropical regions of Asia, Africa, and Central and South America each year, 20 to 50% experience a sudden onset of abdominal cramps, anorexia, and watery diarrhea; thus *traveler's diarrhea* is the most common travel-related illness (Chap. 123). The time of onset is usually 3 days to 2 weeks after the traveler's arrival in a tropical area; most cases begin within the first 3 to 5 days. The illness is generally self-limited, lasting 1 to 5 days. The high rate of diarrhea among travelers to underdeveloped areas is related to the ingestion of contaminated food or water.

The organisms that cause traveler's diarrhea vary considerably with location. In all areas, enterotoxigenic *E. coli* is the most common isolate from persons with the classic

secretory traveler's diarrhea syndrome; the proportion of cases accounted for by this organism ranges from a high of approximately 50% in Latin America to a low of 15% in Asia. *Shigella*, *Salmonella*, and *Campylobacter* spp. are classically considered to cause more invasive dysenteric disease than enterotoxigenic *E. coli*, but clinical differentiation of infections attributable to these organisms can be difficult. *Shigella*, *Salmonella*, and *Campylobacter* are isolated in 1 to 15% of cases, with different organisms being more common in different locations. *Vibrio* spp. are most common in Asia, although *V. cholerae* O1 reached epidemic proportions in parts of Central and South America in 1991 and remains a significant source of concern to travelers to these regions. Epidemic *V. cholerae* O139 Bengal has spread throughout India and Southeast Asia since 1992. Less frequently isolated bacteria are *Aeromonas hydrophila* and *Plesiomonas shigelloides*, which are more common among travelers to Thailand. Parasitic causes of traveler's diarrhea include *Entamoeba histolytica*, which is responsible for up to 5% of cases in Mexico and Thailand, and *G. lamblia*, which has been associated with contaminated freshwater supplies in many areas of the world. *Giardia* is found in association with zoonotic reservoirs in the northern United States and poses a risk to hikers and campers who drink from freshwater streams. A striking association of *Giardia* with contaminated water supplies has likewise been noted in Russia. *Cryptosporidium* has been recognized as a problem in travelers to the former Soviet Republics, Mexico, and Africa and has caused large-scale urban outbreaks of infection in the United States. Disease due to *Cyclospora* and microsporidia has recently been recognized. Viruses such as rotavirus and Norwalk-like viruses have been isolated from as many as 10 to 40% of visitors to areas of Latin America, Asia, and Africa who develop traveler's diarrhea.

**Location** Day-care centers are sites of particularly high attack rates of enteric infections. Rotavirus is most common among children <2 years old, with attack rates of 75 to 100% among those exposed. *G. lamblia* is more common among older children, with somewhat lower attack rates. Other common organisms, often spread by fecal-oral contact, are *Shigella*, *Campylobacter jejuni*, and *Cryptosporidium*. A characteristic feature of infection in day-care centers is the high rate of secondary cases among family members.

Similarly, hospitals are sites for concentrations of enteric infections. In medical intensive-care units and pediatric wards, diarrhea is among the most common nosocomial infections. *C. difficile* is the predominant cause of nosocomial diarrhea among adults in the United States; viral pathogens, especially rotavirus, can spread rapidly in pediatric wards. Enteropathogenic *E. coli* has been associated with outbreaks of diarrhea in nurseries for newborns. One-third of elderly patients in chronic-care institutions develop a significant diarrheal illness each year. Surveillance stool cultures suggest that 25% of the residents of these institutions harbor cytotoxin-producing *C. difficile*, which causes more than half of all cases of diarrhea in this population. Antimicrobial therapy can predispose to pseudomembranous colitis by altering the normal colonic flora and allowing the multiplication of *C. difficile*.

**Age** Most of the morbidity and mortality from enteric pathogens involves children<5 years of age. Breast-fed infants are protected from contaminated food and water and derive some protection from maternal antibodies, but their risk of infection rises dramatically when they begin to eat solid foods. Infants and younger children are more

likely than adults to develop rotaviral disease, while older children and adults are more commonly infected with Norwalk-like viruses. Other organisms with higher attack rates among children than among adults include enterotoxigenic, enteropathogenic, and enterohemorrhagic *E. coli*; *C. jejuni*; and *G. lamblia*. In children, the incidence of *Salmonella* infections is highest among infants<1 year of age, while the attack rate for *Shigella* infections is greatest among children aged 6 months to 4 years.

**Bacterial Food Poisoning** If the history and the stool examination indicate a noninflammatory etiology of diarrhea and there is evidence of a common-source outbreak, questions concerning the ingestion of specific foods and the time of onset of the diarrhea after a meal can provide clues to the bacterial cause of the illness. Potential causes of bacterial food poisoning are shown inTable 131-2.

Bacterial disease caused by an enterotoxin elaborated outside the host, such as that due to *Staphylococcus aureus* or *B. cereus*, has the shortest incubation period (1 to 6 h) and generally lasts <12 h. Most cases of staphylococcal food poisoning are caused by contamination from infected human carriers. Staphylococci can multiply at a wide range of temperatures; thus, if food is left to cool slowly and remains at room temperature after cooking, the organisms will have the opportunity to form enterotoxin. Outbreaks following picnics where potato salad, mayonnaise, and cream pastries have been served offer classic examples of staphylococcal food poisoning. Diarrhea, nausea, vomiting, and abdominal cramping are common, while fever is less so.

*B. cereus* can produce either a syndrome with a short incubation period -- the *emetic* form, mediated by a staphylococcal type of enterotoxin -- or one with a longer incubation period (8 to 16 h) -- the *diarrheal* form, caused by an enterotoxin resembling *E. coli*LT, in which diarrhea and abdominal cramps are characteristic but vomiting is uncommon. The emetic form of *B. cereus* food poisoning is associated with contaminated fried rice; the organism is common in uncooked rice, and its heat-resistant spores survive boiling. If cooked rice is not refrigerated, the spores can germinate and produce toxin. Frying before serving may not destroy the preformed, heat-stable toxin.

Food poisoning due to *C. perfringens* also has a slightly longer incubation period (8 to 14 h) and results from the survival of heat-resistant spores in inadequately cooked meat, poultry, or legumes. After ingestion, toxin is produced in the intestinal tract, causing moderately severe abdominal cramps and diarrhea; vomiting is rare, as is fever. The illness is self-limited, rarely lasting for more than 24 h.

Not all food poisoning has a bacterial cause. Diagnostic confusion can result from diarrhea caused by nonbacterial agents of short-incubation food poisoning, including capsaicin, which is found in hot peppers, and a variety of toxins found in fish and shellfish (Chap. 397).

## LABORATORY EVALUATION

Many cases of noninflammatory diarrhea are self-limited or can be treated empirically, and in these instances the clinician may not need to determine a specific etiology. Potentially pathogenic *E. coli* cannot be distinguished from normal fecal flora by routine culture. Special tests to detectLT andST are not available in most clinical laboratories. In

situations in which cholera is a concern, stool should be cultured on thiosulfate-citrate-bile salts-sucrose (TCBS) agar. A latex agglutination test has made the rapid detection of rotavirus in stool practical for many laboratories, while reverse transcriptase polymerase chain reaction and specific antigen enzyme immunoassays have been developed for the identification of Norwalk-like viruses. At least three stool specimens should be examined for *Giardia* cysts or stained for *Cryptosporidium* if the level of clinical suspicion regarding the involvement of these organisms is high.

All patients with fever and evidence of inflammatory disease acquired outside the hospital should have stool cultured for *Salmonella*, *Shigella*, and *Campylobacter*. *Salmonella* and *Shigella* can be selected on MacConkey's agar as non-lactose-fermenting (colorless) colonies or can be grown on *Salmonella-Shigella* agar or in selenite enrichment broth, both of which inhibit most organisms except these pathogens. Evaluation of nosocomial diarrhea should initially focus on *C. difficile*; stool culture for other pathogens in this setting has an extremely low yield and is not cost-effective. Pathogenic strains of *C. difficile* generally produce two toxins, A and B. Toxin B can be detected with a cytotoxin assay; if the toxin is present, a monolayer culture of fibroblasts will show cytopathic effects within 6 to 24 h. Rapid enzyme immunoassays and latex agglutination tests for both toxin A and toxin B have recently been developed (Chap. 145). Isolation of *C. jejuni* requires inoculation of fresh stool onto selective growth medium and incubation at 42°C in a microaerophilic atmosphere. In many laboratories in the United States, *E. coli* O157:H7 is among the most common pathogens isolated from visible bloody stools. Strains of this enterohemorrhagic serotype can be identified in specialized laboratories by serotyping but also can be identified presumptively as lactose-fermenting, indole-positive colonies of sorbitol nonfermenters (white colonies) on sorbitol MacConkey plates. Fresh stools should be examined for amebic cysts and trophozoites.

## TREATMENT

In many cases, a specific diagnosis is not necessary or not available to guide treatment. The clinician can proceed with the information obtained from the history, stool examination, and evaluation of the severity of dehydration. Empirical regimens for the treatment of traveler's diarrhea are listed inTable 131-3.

The mainstay of treatment is adequate rehydration. The treatment of cholera and other dehydrating diarrheal diseases was revolutionized by the promotion of oral rehydration solutions, the efficacy of which depends on the fact that glucose-facilitated absorption of sodium and water in the small intestine remains intact in the presence of cholera toxin. The use of oral rehydration solutions has reduced mortality due to cholera from>50% (in untreated cases) to<1%. The World Health Organization recommends a solution containing 3.5 g sodium chloride, 2.5 g sodium bicarbonate, 1.5 g potassium chloride, and 20 g glucose (or 40 g sucrose) per liter of water. Patients who are severely dehydrated or in whom vomiting precludes the use of oral therapy should receive intravenous solutions such as Ringer's lactate.

Although most secretory forms of traveler's diarrhea -- usually due to enterotoxigenic *E. coli* -- can be treated effectively with rehydration, bismuth subsalicylate, or antiperistaltic agents, antimicrobial agents can shorten the duration of illness from between 3 and 4

days to between 24 and 36 h.

**PROPHYLAXIS**

Improvements in hygiene to limit fecal-oral spread of enteric pathogens will be necessary if the prevalence of diarrheal diseases is to be significantly reduced in developing countries. Travelers can reduce their risk of diarrhea by eating only hot, freshly cooked food; by avoiding raw vegetables, salads, and unpeeled fruit; and by drinking only boiled or treated water and avoiding ice. In one cross-sectional epidemiologic survey, fewer than 3% of all European and North American travelers to Jamaica adhered to prescribed dietary restrictions, and travel health advice had no impact on the incidence of traveler's diarrhea; overall, the diarrhea attack rate among these travelers was 23.6%, with classic traveler's diarrhea in 11.7%.

Bismuth subsalicylate is an inexpensive agent for the prophylaxis of traveler's diarrhea; it is taken at a dosage of 2 tablets (525 mg) four times a day. Treatment appears to be effective and safe for up to 3 weeks. Prophylactic antimicrobial agents, although effective, are not generally recommended for the prevention of traveler's diarrhea, except when travelers are immunosuppressed or have other underlying illnesses that place them at high risk for morbidity from gastrointestinal infection. The risk of side effects and the possibility of developing an infection with a drug-resistant organism or with more harmful, invasive bacteria make it more reasonable to institute a short course of treatment once symptoms have developed.

The possibility of exerting a major impact on the worldwide morbidity and mortality associated with diarrheal diseases has led to intense efforts to develop effective vaccines against the common bacterial and viral enteric pathogens. Recent research has shown promising advances in the development of vaccines against rotavirus, *Shigella*, *V. cholerae*, *S. typhi*, and enterotoxigenic *E. coli*.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 132. SEXUALLY TRANSMITTED DISEASES: OVERVIEW AND CLINICAL APPROACH - *King K. Holmes*

In all societies, sexually transmitted diseases (STDs) rank among the most common of all infectious diseases, with over 30 infections now classified as predominantly sexually transmitted or as frequently sexually transmissible (Table 132-1). The many new sexually transmitted pathogens recognized and characterized since 1980 include HIV types 1 and 2, human T cell lymphotropic virus (HTLV) types I and II, many genital types of human papillomavirus (HPV), *Mycoplasma genitalium*, two species of *Mobiluncus* (associated with bacterial vaginosis), two species of *Helicobacter* (initially associated with proctocolitis in homosexual men and later, during the AIDS era, with bacteremia, dermatitis, and fever among immunosuppressed individuals), and the Kaposi's sarcoma-associated herpesvirus (human herpesvirus type 8, or HHV-8).

In developing countries, with three-quarters of the world's population and 90% of the world'sSTDs, such factors as population growth (especially in adolescent and young-adult age groups), rural-to-urban migration, wars, and poverty create exceptional vulnerability to disease resulting from risky sexual behaviors. This situation leads to the spread of STD, with the emergence of new pathogens and new variants of old pathogens. During the 1990s, in China, Russia, the states of the former Soviet Union, and South Africa, internal social structures changed rapidly as borders opened to the West, unleashing enormous new epidemics of HIV infection and other STDs. HIV has become the leading cause of death in some developing countries, andHPV and hepatitis B virus (HBV) remain important causes of cervical and hepatocellular carcinoma, respectively -- two of the commonest malignancies in the developing world. Sexually transmitted herpes simplex virus (HSV) infections now cause most genital ulcer disease throughout the world and an increasing proportion of cases of genital herpes in developing countries with generalized HIV epidemics, where the positive feedback loop between HSV and HIV transmission is a growing, intractable problem. Globally, the agents of curable STDs -- gonorrhea, chlamydial infections, syphilis, chancroid, and trichomoniasis -- caused ~350 million new infections annually in the mid-1990s. Bacterial vaginosis (arguably acquired sexually) occurs in up to 50% of women of reproductive age in developing countries. Thus, there are probably close to 1 billion cases of these curable infections annually, all six of which are associated with increased risk of HIV transmission or acquisition.

In the industrialized countries, fear of HIV infection since the mid- 1980s, coupled with widespread behavioral interventions and better- organized systems of care for the curableSTDs, have helped curb the transmission of the latter diseases. Nonetheless, viral STDs, such as genital herpes andHPVinfection, had not obviously decreased in incidence at the turn of the millennium, and infection with HIV remains a leading cause of death in persons 25 to 44 years of age in the United States, as in developing countries, despite the advent of potent antiretroviral therapy.

Although rates of the bacterialSTDshave fallen in all industrialized countries over the past 20 years, foci of hyperendemic transmission persist in the southeastern United States and in most large U.S. cities. Rates of gonorrhea and syphilis remain higher in the United States than in any other Western industrialized country. The reemergence of syphilis and gonorrhea epidemics in Russia and the former Soviet states has created

similar foci for reintroduction of these STDs into western Europe. The remarkable return of high rates of gonorrhea and syphilis among homosexual and bisexual men in many parts of the United States reflects increased risk-taking since the advent of potent antiretroviral therapy and may portend resurgent transmission of HIV in this group.

## CLASSIFICATION AND EPIDEMIOLOGY

Sexually transmitted infection (STI) may or may not result in disease (STD). Some prefer the term *reproductive tract infection* to destigmatize the diagnosis and treatment of STIs and to encompass conditions such as bacterial vaginosis, whose designation as an STD is debated.

CertainSTDs(such as syphilis, gonorrhea, HIV infection, hepatitis B, and chancroid) are most concentrated within "core populations" having high rates of partner change, concurrent partners, or "dense" sexual networks -- for example, prostitutes and their clients and persons involved in the use of illicit drugs, particularly crack cocaine. Poor access to or low motivation for obtaining early treatment also fosters spread of the curable STIs. In most of the United States, groups most vulnerable to STDs, including HIV infection, consist predominantly of young unmarried individuals of low socioeconomic status who often reside within crowded urban neighborhoods, although some rural areas (e.g., in the southeastern United States) also have high rates of STIs. Other STDs are distributed more evenly in society. For example, chlamydial infections can persist for many months, often asymptomatically, and can propagate widely in populations that do not share all of the characteristics of core groups described above. Similarly, genitalHPVinfections and genital herpes persist and spread efficiently in relatively low-risk populations.

In general, the product of three factors determines the initial rate of spread of anySTIwithin a population: rate of exposure, efficiency of transmission per exposure, and duration of infectivity of those infected. Efforts to prevent and control STIs attempt to decrease the duration of infectivity (through early diagnosis and curative or suppressive treatment), to decrease the efficiency of transmission (e.g., through promotion of condom use and safer sexual practices), and to decrease the rate of exposure of susceptibles to infected persons (e.g., through provision of information, health education, and counseling and efforts to change the norms of sexual behavior).

## MANAGEMENT OF COMMON STD SYNDROMES

Although other chapters discuss management of specificSTIs, delineating treatment based on diagnosis of a specific infection, most patients are actually managed (at least initially) on the basis of presenting symptoms and signs and associated risk factors, even in industrialized countries.Table 132-2 lists some of the most common clinicalSTDsyndromes and their microbial etiologies. Strategies for their management are outlined below. Chaps. 191 and309address the management of infections with human retroviruses.

### RISK ASSESSMENT

Routine patient care begins with risk assessment (e.g., for heart disease, cancer). An

overall risk assessment interview should include STD/HIV in primary care, urgent care, and emergency care settings as well as in specialty clinics providing adolescent, prenatal, and family planning services. STD/HIV risk assessment guides interpretation of symptoms that could reflect an STD; decisions on screening or prophylactic/preventive treatment; risk reduction counseling and intervention (e.g., hepatitis B vaccination); and notification of partners of patients with known infections. Consideration of routine demographic data (e.g., gender, age, marital status, area of residence) is a simple first step in STD/HIV risk assessment. For example, national guidelines recommend routine screening of sexually active females £25 years of age for *C. trachomatis* infection. Table 132-3 provides a set of 10 STD/HIV risk assessment questions that clinicians can pose verbally or that health care systems can adapt (with yes/no responses) into a routine self-administered questionnaire for use in clinics. The initial framing statement gives permission to discuss taboo topics.

Risk assessment is followed by clinical assessment (elicitation of information on specific current symptoms and signs of STDs). Confirmatory diagnostic tests (for those with symptoms or signs) or screening tests (for those without symptoms or signs) may involve microscopic examination, culture, antigen detection tests, genetic probe or amplification tests, or serology. Initial syndrome-based treatment should cover the most likely causes. For certain syndromes, results of rapid tests can narrow the spectrum of this initial therapy (e.g., wet mount of vaginal fluid for women with vaginal discharge, Gram's stain of urethral discharge for men with urethral discharge, rapid plasma reagin test for genital ulcer). After the institution of treatment, STD management proceeds to the "4 C's" of prevention and control: *c*ontact tracing (see "Prevention and Control of STDs," below), ensuring *c*ompliance with therapy, and *c*ounseling on risk reduction, including *c*ondom promotion and provision.

**URETHRITIS IN MEN**

The incidence of reported gonococcal urethritis (Fig. 145-CD1) in the United States has fallen to the lowest level since reporting began, while that of nongonococcal urethritis (NGU) remains high -- a pattern typical of all industrialized countries. Until recently, *Chlamydia trachomatis* caused ~30 to 40% of NGU cases, but the proportion of cases due to this organism may have declined in some populations served by effective chlamydial control programs.HSV and *Trichomonas vaginalis* each cause a small proportion of NGU cases in the United States. Case-control studies have also implicated *Ureaplasma urealyticum* and *M. genitalium* as probable causes of many *Chlamydia*-negative cases, and coliform bacteria can cause urethritis in men who practice insertive anal intercourse. The initial diagnosis of urethritis in men currently includes specific tests only for *Neisseria gonorrhoeae* and *C. trachomatis*. Table 132-4 summarizes the steps in management of sexually active men with symptoms of urethral discharge and/or dysuria.

1. *Establish the presence of urethritis*. If proximal-to-distal "milking" of the urethra does not express a purulent or mucopurulent discharge, even after the patient has not voided for several hours or preferably overnight, the centrifuged sediment of the first 20 to 30 mL of voided urine can be examined for inflammatory cells, either by microscopy or by the leukocyte esterase test. In urethral gonococcal or chlamydial infection, a Gram's-stained smear of overt discharge or of an anterior urethral specimen obtained

by passage of a small urethrogenital swab 2 to 3 cm into the urethra usually reveals ³5 neutrophils per 1000´ field in areas containing cells; in gonococcal infection, such a smear also usually reveals gram-negative intracellular diplococci. Patients with symptoms who lack objective evidence of urethritis may have functional rather than organic problems and generally do not benefit from repeated courses of antibiotics.

2. *Evaluate for complications or alternative diagnoses*. A brief history and examination will exclude epididymitis and systemic complications, such as disseminated gonococcal infection and Reiter's syndrome. Although digital examination of the prostate gland seldom contributes to the evaluation of sexually active young men with urethritis, men with dysuria who lack evidence of urethritis as well as sexually inactive men with urethritis should undergo prostate palpation, urinalysis, and urine culture to exclude bacterial prostatitis and cystitis.

3. *Evaluate for gonococcal and chlamydial infection*. An absence of typical gram-negative diplococci on Gram's-stained smear of urethral exudate containing inflammatory cells warrants a preliminary diagnosis ofNGU and should lead to testing of the urethral specimen for *C. trachomatis*. Culture or DNA detection tests for *N. gonorrhoeae* may be positive when Gram's staining is negative; certain strains of *N. gonorrhoeae* reportedly can result in negative urethral Gram's stains in up to 30% of cases of urethritis. Results of tests for gonococcal and chlamydial infection predict the patient's prognosis (with greater risk for recurrent NGU if neither chlamydiae nor gonococci are found than if either is detected) and can guide both the counseling given to the patient and the management of the patient's sexual partner(s).

4. *Treat urethritis*.

## TREATMENT

In practice, if Gram's stain does not reveal gonococci, urethritis is treated with a regimen effective forNGU, such as azithromycin (1.0 g orally in a single dose). If gonococci are demonstrated by Gram's stain or if no diagnostic tests are performed to definitively exclude gonorrhea, treatment should also include a single-dose regimen for gonorrhea (Chap. 147). Sexual partners should be tested for gonorrhea and chlamydial infection and should receive the same regimen given to the male index case.

## EPIDIDYMITIS

Acute epididymitis, almost always unilateral, must be differentiated from testicular torsion, tumor, and trauma. Torsion, a surgical emergency, usually occurs in the second or third decade of life and produces a sudden onset of pain, elevation of the testicle within the scrotal sac, rotation of the epididymis from a posterior to an anterior position, and absence of blood flow on Doppler examination or$^{99m}$Tc scan. Persistence of symptoms after a course of therapy for epididymitis suggests the possibility of testicular tumor. In sexually active men under age 35, acute epididymitis is caused most frequently by *C. trachomatis* and less commonly by *N. gonorrhoeae* and is usually associated with overt or subclinical urethritis. Acute epididymitis in older men or following urinary tract instrumentation is usually caused by urinary pathogens. Similarly, epididymitis in men who have practiced insertive rectal intercourse is often caused by

Enterobacteriaceae. These men usually have no urethritis but do have bacteriuria.

## TREATMENT

Ofloxacin (300 mg orally bid for 10 days) is an optimal agent for syndrome-based treatment of epididymitis because of its effectiveness against *N. gonorrhoeae*, *C. trachomatis*, and Enterobacteriaceae. Alternatively, ceftriaxone (250 mg intramuscularly) followed by doxycycline (100 mg orally bid for 10 days) is effective for epididymitis caused by *N. gonorrhoeae* or *C. trachomatis*.

## URETHRITIS AND THE URETHRAL SYNDROME IN WOMEN

*C. trachomatis*, *N. gonorrhoeae*, and occasionallyHSVcause symptomatic urethritis -- known as the urethral syndrome in women -- characterized by "internal" dysuria (usually without urinary urgency or frequency) and pyuria, with *Escherichia coli* or other uropathogens not present in urine at counts of£$10^2$/mL. In contrast, the dysuria associated with vulvar herpes or vulvovaginal candidiasis (and perhaps with trichomoniasis) is often described as "external," being caused by painful contact of urine with the inflamed or ulcerated labia or introitus. Acute onset, association with urinary urgency or frequency, hematuria, or suprapubic bladder tenderness suggests bacterial cystitis. Among women with symptoms of acute bacterial cystitis, costovertebral pain and tenderness or fever suggests acute pyelonephritis. The management of bacterial urinary tract infection (UTI) is discussed inChap. 280.

Signs of vulvovaginitis, coupled with symptoms of external dysuria, suggest vulvar infection (e.g., withHSV or *Candida albicans*). Among dysuric women without signs of vulvovaginitis, bacterialUTI must be differentiated from the urethral syndrome by assessment of risk, evaluation of the pattern of symptoms and signs, and specific microbiologic testing. AnSTDetiology of the urethral syndrome is suggested by young age, more than one current sexual partner or a new partner within the past month, or coexisting mucopurulent cervicitis (MPC; see below). The finding of a single urinary pathogen, such as *E. coli* or *Staphylococcus saprophyticus*, at a concentration of$^3$$10^2$/mL in a properly collected specimen of midstream urine from a dysuric woman with pyuria indicates probable bacterial UTI, whereas pyuria with<$10^2$conventional uropathogens per milliliter of urine ("sterile" pyuria) suggests acute urethral syndrome due to *C. trachomatis* or *N. gonorrhoeae*. Gonorrhea and chlamydial infection should be sought by specific tests. Among women with sterile pyuria caused by chlamydial infection, treatment with doxycycline (100 mg bid for 7 days) alleviates dysuria.

## VULVOVAGINAL INFECTIONS

**Abnormal Vaginal Discharge** If directly questioned during routine health checkups, many women acknowledge having nonspecific symptoms of vaginal discharge that do not correlate with objective signs of inflammation or with actual infection. However, unsolicited reporting of abnormal vaginal discharge does suggest bacterial vaginosis or trichomoniasis. Specifically, an abnormally increased amount, an abnormal odor, and an abnormal yellow color of the discharge are associated with one or both of these conditions. Cervical infection with *N. gonorrhoeae* or *C. trachomatis* does not appear to cause an increased amount or abnormal odor of discharge, but cervicitis, like

trichomoniasis, can include the production of an increased number of neutrophils in vaginal fluid, resulting in a yellow color. Vulvar conditions such as genital herpes or vulvovaginal candidiasis can cause vulvar pruritus, burning, irritation, or lesions as well as external dysuria (as urine passes over the inflamed vulva) or vulvar dyspareunia.

Certain vulvovaginal infections may have serious sequelae. Trichomoniasis, bacterial vaginosis, and vulvovaginal candidiasis have all been associated with increased risk of acquisition of HIV infection. Vaginal trichomoniasis and bacterial vaginosis early in pregnancy independently predict premature onset of labor. Bacterial vaginosis can also lead to anaerobic bacterial infection of the endometrium and salpinges. Vaginitis may be an early and prominent feature of toxic shock syndrome, and recurrent or chronic vulvovaginal candidiasis develops with increased frequency among women with systemic illnesses, such as diabetes mellitus or HIV-related immunosuppression (although only a very small proportion of women with recurrent vulvovaginal candidiasis in the United States actually have a serious predisposing illness).

Thus vulvovaginal symptoms or signs warrant careful evaluation, including pelvic examination, simple rapid diagnostic tests, and appropriate therapy specific for the anatomic site and type of infection. Unfortunately, a recent survey in the United States indicated that clinicians seldom perform the tests required to establish the cause of such symptoms. The diagnosis and treatment of the three most common types of vaginal infection are summarized inTable 132-5.

Inspection of the vulva and perineum may reveal tender genital ulcerations (typically due to HSVinfection, occasionally to chancroid) or fissures (typically due to vulvovaginal candidiasis) or discharge visible at the introitus before insertion of a speculum (suggestive of bacterial vaginosis or trichomoniasis). Speculum examination permits the clinician to discern whether the discharge in fact looks abnormal and whether any abnormal discharge in the vagina emanates from the cervical os (mucoid and, if abnormal, yellow) or from the vagina (not mucoid, since the vaginal epithelium does not produce mucus). Symptoms or signs of abnormal vaginal discharge should prompt testing of vaginal fluid for pH, odor when mixed with 10% KOH, and microscopic features when mixed with saline and with 10% KOH. Additional objective laboratory tests useful for establishing the cause of abnormal vaginal discharge include Gram's staining to detect alterations in the vaginal flora; new card and dipstick tests for bacterial vaginosis, as described below; and a new DNA probe test purported to detect *T. vaginalis* and *C. albicans* as well as the increased concentrations of *Gardnerella vaginalis* associated with bacterial vaginosis.

## TREATMENT

Patterns of treatment for vaginal discharge vary widely. In developing countries, where clinics or pharmacies often dispense treatment based on symptoms alone without examination or testing, oral treatment with metronidazole, either as a 2-g single dose or as a 7-day regimen, provides reasonable coverage against both trichomoniasis and bacterial vaginosis, the usual causes of symptoms of vaginal discharge; metronidazole treatment of sex partners would prevent reinfection of women with trichomoniasis even if it does not help prevent the recurrence of bacterial vaginosis. Guidelines promulgated during the 1990s by the World Health Organization suggested treatment for cervical

infection and for vulvovaginal candidiasis in women with symptoms of abnormal vaginal discharge; in retrospect, these recommendations were faulty, since these conditions seldom produce such symptoms.

In industrialized countries, clinicians treating symptoms and signs of abnormal vaginal discharge should at least differentiate between bacterial vaginosis and trichomoniasis, because optimal management of patients and partners differs for these two conditions, as discussed briefly below.

**Vaginal Trichomoniasis (See also Chap. 218)** Symptomatic trichomoniasis characteristically produces a profuse, yellow, purulent, homogeneous vaginal discharge and vulvar irritation, often with visible inflammation of the vaginal and vulvar epithelium and petechial lesions on the cervix (the so-called strawberry cervix, usually evident only by colposcopy). The pH of vaginal fluid usually rises to $^{3}$5.0. In women with typical symptoms and signs of trichomoniasis, microscopic examination of vaginal discharge mixed with saline reveals motile trichomonads in at least 80% of culture-positive cases. However, in the absence of symptoms or signs, culture is often required for detection of the organism. Treatment of asymptomatic as well as symptomatic cases reduces rates of transmission and prevents later development of symptoms.

**TREATMENT**

Only nitroimidazoles consistently cure trichomoniasis. Tinidazole and ornidazole have longer half-lives than metronidazole but do not give better results than a single 2-g oral dose of metronidazole, the treatment of choice. Treatment of male sexual partners -- often facilitated by dispensing metronidazole to the female patient to give to her partner(s), with a warning about avoiding the concurrent use of alcohol -- reduces both the risk of reinfection and the reservoir of infection. Treatment with 0.75% metronidazole gel intravaginally, although effective for bacterial vaginosis, is not reliable for vaginal trichomoniasis. Systemic use of metronidazole is not recommended during the first trimester of pregnancy but is considered safe thereafter.

**Bacterial Vaginosis** This syndrome (formerly termed *nonspecific vaginitis*, *Haemophilus vaginitis*, *anaerobic vaginitis*, or *Gardnerella-associated vaginal discharge*) is characterized by symptoms of vaginal malodor and a slightly to moderately increased white discharge, which appears homogeneous, is low in viscosity, and smoothly coats the vaginal mucosa. Risk factors include multiple sexual partners and recent intercourse with a new partner, but antibiotic treatment of male partners has not reduced the rate of recurrence among affected women.

The vaginal fluid of women with bacterial vaginosis is characterized by markedly increased prevalences and concentrations of *G. vaginalis*, *Mycoplasma hominis*, and several anaerobic bacteria [e.g., *Mobiluncus* spp., *Prevotella* spp. (formerly *Bacteroides* spp.), and some *Peptostreptococcus* spp.]. The vaginal fluid usually lacks hydrogen peroxide-producing *Lactobacillus* spp., which constitute most of the normal vaginal flora and perhaps help protect against certain cervical and vaginal infections. Vaginal douching, use of intravaginal nonoxynol-9 spermicide, and new sexual partners can all result in loss of vaginal colonization by hydrogen peroxide-producing lactobacilli.

Bacterial vaginosis is conventionally diagnosed clinically with the *Amsel criteria*, which include any three of the following four clinical abnormalities: (1) objective signs of increased white homogeneous vaginal discharge; (2) a vaginal discharge pH of >4.5; (3) liberation of a distinct fishy odor (attributable to volatile amines such as trimethylamine) immediately after vaginal secretions are mixed with a 10% solution of KOH; and (4) microscopic demonstration of "clue cells" (vaginal epithelial cells coated with coccobacillary organisms giving them a granular appearance and indistinct borders; Fig. 132-1) on a wet mount prepared by mixing vaginal secretions with normal saline in a ratio of ~1:1. A new card test now facilitates screening of vaginal fluid for pH >4.5 and trimethylamine, and a new dipstick test detects proline aminopeptidase, an enzyme associated with this syndrome.

Alternatively, the microbiology laboratory can determine the *Nugent score* by examining a Gram-stained smear of vaginal discharge. A score of 7 to 10, based on reduced numbers or the absence of large gram-positive rods (lactobacilli) and the presence of small gram-negative or variable rods (*Gardnerella* and anaerobic rods) and of curved gram-negative or variable rods (*Mobiluncus*), has high sensitivity and specificity for the diagnosis of bacterial vaginosis. Attempts to isolate *G. vaginalis*, genital mycoplasmas, or anaerobic bacteria do not aid in the diagnosis of bacterial vaginosis because these organisms occur (albeit in much lower concentrations) in the vaginal flora of many women without the syndrome.

## TREATMENT

The standard dosage of metronidazole for the treatment of bacterial vaginosis is 500 mg orally bid for 7 days. Alternatively, the single 2-g oral dose of metronidazole recommended for trichomoniasis produces short-term rates of recurrence of bacterial vaginosis somewhat higher than those obtained with the 7-day regimen. Intravaginal treatment with 2% clindamycin cream [one full applicator (5 g containing 100 mg of clindamycin phosphate) each night for 7 nights] or with 0.75% metronidazole gel [one full applicator (5 g containing 37.5 mg of metronidazole) twice daily for 5 days] is also effective and does not elicit systemic adverse reactions. Nonetheless, long-term recurrence (i.e., after several months) is distressingly common after either oral or intravaginal treatment. Treatment of male partners with metronidazole does not prevent recurrence of bacterial vaginosis, even though new sexual partners have been implicated as a risk factor for recurrence.

No controlled data support the use of currently available vaginal or oral preparations of lactobacilli for the treatment or prevention of recurrence of bacterial vaginosis. Clinical trials are evaluating prevention of recurrence by repeated intravaginal inoculation of a vaginal *Lactobacillus* species that produces hydrogen peroxide and adheres to vaginal epithelium.

**Vulvovaginal Pruritus, Burning, or Irritation** Vulvovaginal candidiasis produces vulvar pruritus, burning, or irritation, generally without symptoms of increased vaginal discharge or malodor. Genital herpes can produce similar symptoms, with lesions sometimes difficult to distinguish from the fissures caused by candidiasis. Signs of vulvovaginal candidiasis include vulvar erythema, edema, fissures, and tenderness. With candidiasis, a white scanty vaginal discharge sometimes takes the form of white

thrushlike plaques or cottage cheese- like curds adhering loosely to the vaginal mucosa. *C. albicans* accounts for nearly all cases of symptomatic vulvovaginal candidiasis, which probably arise from endogenous strains of *C. albicans* that have colonized the vagina or the intestinal tract.

The diagnosis of vulvovaginal candidiasis usually involves the demonstration of pseudohyphae or hyphae by microscopic examination of vaginal fluid mixed with saline or 10% KOH or subjected to Gram's staining. Microscopic examination is less sensitive than culture but correlates better with symptoms.

## TREATMENT

Symptoms and signs of vulvovaginal candidiasis warrant treatment, usually intravaginal administration of any of several imidazole antibiotics (e.g., miconazole or clotrimazole) for 3 to 7 days. Over-the-counter marketing of such preparations has reduced the cost of care and made treatment more convenient for many women with recurrent yeast vulvovaginitis. However, most women who purchase these preparations do not have vulvovaginal candidiasis, while many do have other vaginal infections that require different treatment. Therefore, only women with classic symptoms of vulvar pruritus and a history of previous episodes of yeast vulvovaginitis documented by an experienced clinician should self-treat. Single-dose oral treatment with fluconazole (150 mg) is also effective and is preferred by many patients. Prolonged or periodic oral therapy may benefit women with severe or frequently recurrent vulvovaginal candidiasis and those who do not respond to intravaginal or single-dose oral therapy. Such patients probably should be evaluated for diabetes and HIV infection, although such systemic illnesses seldom explain recurrent vulvovaginal candidiasis. Treatment of sexual partners is not routinely indicated.

**Other Causes of Vaginal Discharge or Vaginitis** In the ulcerative vaginitis associated with staphylococcal toxic shock syndrome, *Staphylococcus aureus* should be promptly identified in vaginal fluid by Gram's stain and by culture. In desquamative inflammatory vaginitis, smears of vaginal fluid reveal neutrophils, massive vaginal epithelial cell exfoliation with increased numbers of parabasal cells, and gram-positive cocci; this syndrome responds to treatment with 2% clindamycin cream. Additional causes of vaginitis and vulvovaginal symptoms in women include retained foreign bodies (e.g., tampons), cervical caps, vaginal spermicides, vaginal antiseptic preparations or douches, vaginal epithelial atrophy in postmenopausal women or in the postpartum period during prolonged breast-feeding, allergic reactions to latex condoms, vaginal aphthae associated with HIV infection or Behcet's syndrome, and vestibulitis (a poorly understood syndrome).

## MUCOPURULENT CERVICITIS

MPCrefers to inflammation of the columnar epithelium and subepithelium of the endocervix and of any contiguous columnar epithelium that lies exposed in an ectopic position on the exocervix. MPC in women represents the "silent partner" of urethritis in men, being equally common and often caused by the same agents (*N. gonorrhoeae* or *C. trachomatis*) but more difficult to recognize. As the most common manifestation of these serious bacterial infections in women, MPC can be a harbinger or sign of pelvic

inflammatory disease (PID) and -- in pregnant women -- can lead to obstetric complications. More than half of all cases of this syndrome in the United States today remain idiopathic.

The diagnosis ofMPCrests on the detection of yellow mucopurulent discharge from the cervical os or of increased numbers of polymorphonuclear leukocytes in Gram-stained or Papanicolaou-stained smears of endocervical mucus. MPC due to *C. trachomatis* can also produce edematous cervical ectopy (see below) and endocervical bleeding upon gentle swabbing. Unlike the endocervicitis produced by gonococcal or chlamydial infection, cervicitis caused byHSVproduces ulcerative lesions on the stratified squamous epithelium of the exocervix as well as on the columnar epithelium. Yellow cervical mucus on a white swab removed from the endocervix indicates the presence of polymorphonuclear leukocytes. The mucus should be rolled thinly on a slide for Gram's staining. The presence of ³20 polymorphonuclear cells per 1000´ microscopic field within strands of cervical mucus not contaminated by vaginal squamous epithelial cells or vaginal bacteria indicates endocervicitis (Fig. 132-2). Detection of intracellular gram-negative diplococci in carefully collected endocervical mucus is quite specific but£50% sensitive for gonorrhea. Therefore, specific and sensitive tests for *N. gonorrhoeae* as well as *C. trachomatis* are also indicated in evaluation of MPC.

## TREATMENT

Although the above criteria forMPC are neither highly specific nor highly predictive of gonococcal or chlamydial infection in many settings, current guidelines of the Centers for Disease Control and Prevention call for consideration of empirical treatment for MPC, pending test results, "for a patient who has suspected gonorrhea or chlamydial infection, if the prevalences of these infections are high in the patient population, and the patient might be difficult to locate after treatment." In this situation, therapy should include a single-dose regimen effective for gonorrhea plus treatment for chlamydial infection, as outlined inTable 132-4 for treatment of urethritis. In settings where gonorrhea is much less common than chlamydial infection, initial therapy for chlamydial infection alone suffices. The etiology and potential benefit of treatment of endocervicitis not associated with gonorrhea or chlamydial infection remain undefined. Sexual partner(s) of a woman with MPC should be examined and given a regimen similar to that chosen for the woman unless results of tests for gonorrhea or chlamydial infection in either partner warrant different therapy or no therapy.

## CERVICAL ECTOPY

Cervical ectopy, often mislabeled "cervical erosion," is easily confused with infectious endocervicitis. Ectopy represents the presence of the one-cell-thick columnar epithelium extending from the endocervix out onto the visible ectocervix. In ectopy, the cervical os may contain clear or slightly cloudy mucus but usually not yellow mucopus. Colposcopy shows intact epithelium. Normally found during adolescence and early adulthood, ectopy gradually recedes through the second and third decades of life, as squamous metaplasia replaces the ectopic columnar epithelium. Oral contraceptive use favors the persistence or reappearance of ectopy, while smoking apparently accelerates squamous metaplasia. Cauterization for the elimination of ectopy is not warranted. Ectopy may render the cervix more susceptible to infection with *N. gonorrhoeae*, *C.*

*trachomatis*, or HIV by exposing a larger area of susceptible columnar epithelium on the exocervix.

**PELVIC INFLAMMATORY DISEASE SeeChap. 133.**

**ULCERATIVE GENITAL LESIONS**

Genital ulceration reflects a set of importantSTIs, most of which also sharply increase the risk of sexual acquisition and shedding of HIV. Accurate diagnosis, treatment, and prevention of these infections are high priorities. In a study of genital ulcers carried out in 1996 in 10 of the U.S. cities with the highest rates of primary syphilis, polymerase chain reaction (PCR) testing of ulcer specimens demonstratedHSV in 62% of patients, *Treponema pallidum* in 13%, and *Haemophilus ducreyi* in 12 to 20%.

In Asia and Africa, chancroid (Fig. 132-CD1)was once considered the most common type of genital ulcer, followed by primary syphilis and then genital herpes. With increased efforts to control chancroid and syphilis, together with more frequent recurrences or persistence of genital herpes attributable to the growing numbers of immunosuppressed persons with HIV infection,PCRtesting of genital ulcers now clearly implicates genital herpes as the most common cause of genital ulceration in some developing countries. Lymphogranuloma venereum (LGV) (Fig. 132-CD2) and donovanosis (granuloma inguinale;Fig. 132-CD3) continue to cause genital ulceration in developing countries but rarely occur today in North America or Europe. Other causes of genital ulcer include (1) candidiasis and traumatized genital warts -- both readily recognized; (2) lesions due to genital involvement of more widespread dermatoses; and (3) cutaneous manifestations of systemic diseases, such as genital mucosal ulceration in Stevens-Johnson syndrome.

Although most genital ulcerations cannot be diagnosed confidently on clinical grounds alone, clinical findings plus epidemiologic considerations (Table 132-6) can usually guide initial management (Table 132-7) pending results of further tests. Clinicians should order a rapid serologic test for syphilis in all cases of genital ulcer and a dark-field, direct immunofluorescence, orPCR test for *T. pallidum* from all lesions except those highly characteristic of infection withHSV(i.e., those with herpetic vesicles).

Typical vesicles or pustules or a cluster of painful ulcers preceded by vesiculopustular lesions suggests genital herpes. These typical clinical presentations make detection of the virus optional; however, many patients want confirmation of the diagnosis, and differentiation ofHSV-1 from HSV-2 has prognostic implications, since the latter causes more frequent recurrences.

Painless, nontender, indurated ulcers with firm, nontender inguinal adenopathy suggest primary syphilis. If the results of dark-field examination and a rapid serologic test for syphilis are initially negative and the patient will comply with follow-up and sexual abstinence, the performance of two more dark-field examinations on successive days before treatment is begun will improve the sensitivity of diagnosis of syphilis, as will repeated serologic testing for syphilis 1 or 2 weeks later.

"Atypical" or clinically trivial ulcers may be more common manifestations of genital

herpes than classic vesiculopustular lesions. Specific tests forHSV in the lesions are therefore indicated (Chap. 182). Type-specific serologic tests for serum antibody to HSV-2, now commercially available, may give negative results, especially when patients present early with the initial episode of genital herpes or when HSV-1 is the cause of genital herpes (as in 15 to 30% of cases today). Furthermore, a positive test for HSV-2 antibody does not prove that the current lesions are herpetic, since nearly one-fourth of the general population of the United States becomes seropositive for HSV-2 during early adulthood. Nonetheless, a positive HSV-2 serology does enable the clinician to tell the patient that he or she has had genital herpes, should learn to recognize symptoms, should avoid sex during recurrences, and should consider use of condoms at other times.

Demonstration of *H. ducreyi* by culture (or byPCRtest, when available) is most useful when ulcers are painful and purulent, especially when inguinal lymphadenopathy with fluctuance or overlying erythema is noted; if chancroid is prevalent in the community; or if the patient has recently had a sexual exposure in a chancroid-endemic area (e.g., a developing country or certain North American cities). Enlarged, fluctuant lymph nodes should be aspirated for culture or PCR tests to detect *H. ducreyi* as well as for Gram's staining and culture to rule out the presence of other pyogenic bacteria.

When genital ulcers persist beyond the natural history of initial episodes of herpes (2 to 3 weeks) or of chancroid or syphilis (up to 6 weeks) and do not resolve with syndrome-based antimicrobial therapy, then -- in addition to the usual tests for herpes, syphilis, and chancroid -- biopsy is indicated to exclude donovanosis, carcinoma, and other nonvenereal dermatoses. HIV serology should also be undertaken, since chronic, persistent genital herpes is common in AIDS.

Immediate syndrome-based treatment for acute genital ulcerations (after collection of all necessary diagnostic specimens) is often appropriate. Patients with typical initial or recurrent episodes of genital or anorectal herpes can benefit from prompt oral antiviral therapy (Chap. 182). The patient with nonvesicular ulcerative lesions who may not return for follow-up or may continue sexual activity should receive initial treatment for syphilis, together with empirical therapy for chancroid if exposed in an area where chancroid occurs or if regional lymph node suppuration is evident. In resource-poor settings lacking ready access to diagnostic tests, this approach to syndromic treatment for syphilis and chancroid has helped bring these two diseases under better control. Finally, empirical antimicrobial therapy may be indicated if ulcers persist and the diagnosis remains unclear after a week of observation despite attempts to diagnose herpes, syphilis, and chancroid.

## PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, AND ENTERITIS

Sexually acquired proctitis, with inflammation limited to the rectal mucosa, results from direct rectal inoculation of typicalSTDpathogens. In contrast, inflammation extending from the rectum to the colon (proctocolitis), involving both the small and the large bowel (enterocolitis), or involving the small bowel alone (enteritis) can result from ingestion of typical intestinal pathogens through oral-anal exposure during sexual contact. Anorectal pain and mucopurulent, bloody rectal discharge suggest proctitis or protocolitis. Proctitis commonly produces tenesmus (causing frequent attempts to defecate, but not true

diarrhea) and constipation, whereas proctocolitis and enterocolitis more often cause true diarrhea. In all three conditions, anoscopy usually shows mucosal exudate and easily induced mucosal bleeding (i.e., a positive "wipe test"), sometimes with petechiae or mucosal ulcers. Exudate should be sampled for Gram's staining and other microbiologic studies. Sigmoidoscopy or colonoscopy shows inflammation limited to the rectum in proctitis or disease extending at least into the sigmoid colon in proctocolitis.

The AIDS era has brought an extraordinary shift in the clinical and etiologic spectrum of intestinal infections among homosexual men. The number of cases of the acute intestinalSTIsdescribed above has fallen as high-risk sexual behaviors have become less common in this group. At the same time, the number of AIDS-related opportunistic intestinal infections has risen rapidly, many associated with chronic or recurrent symptoms. Acquisition of *N. gonorrhoeae*,HSV, or *C. trachomatis* during receptive anorectal intercourse causes most cases of infectious proctitis. Primary and secondary syphilis can also produce anal or anorectal lesions, with or without symptoms. Gonococcal or chlamydial proctitis typically involves the most distal rectal mucosa and the anal crypts and is clinically mild, without systemic manifestations. In contrast, primary proctitis due to HSV and proctocolitis due to the strains of *C. trachomatis* that causeLGVusually produce severe anorectal pain and often cause fever. Perianal ulcers and inguinal lymphadenopathy, most commonly due to HSV, can also occur in LGV or syphilis. Sacral nerve root radiculopathies, usually presenting as urinary retention, laxity of the anal sphincter, or constipation, may complicate primary herpetic proctitis. In LGV, rectal biopsy typically shows crypt abscesses, granulomas, and giant cells -- findings resembling those in Crohn's disease; such findings should always prompt rectal culture and serology for LGV, which is a curable infection. Syphilis can also produce rectal granulomas, usually in association with infiltration by plasma cells or other mononuclear cells.

Diarrhea and abdominal bloating or cramping pain without anorectal symptoms and with normal findings on anoscopy and sigmoidoscopy occur with inflammation of the small intestine (enteritis) or with proximal colitis. In homosexual men without HIV infection, enteritis is often attributable to *Giardia lamblia*. Sexually acquired proctocolitis is most often due to *Campylobacter* or *Shigella* spp.

## PREVENTION AND CONTROL OF STDS

Although rates of all curableSTDsfell in the United States throughout the 1990s, all other industrialized countries of comparable economic development have made greater progress. For example, Sweden has virtually eliminated the transmission of gonorrhea, syphilis, and chancroid and has achieved very low rates of HIV transmission. Elimination of syphilis as an endemic disease is now a national goal in the United States, but stronger efforts toward prevention and control of all STDs are necessary.

Prevention and control ofSTDsrequire (1) reduction of the average rate of sexual exposure through alteration of behaviors and behavioral norms among both susceptible and infected persons in all population groups; (2) reduction of the efficiency of transmission through the promotion of safer sexual practices, the use of condoms during casual or commercial sex, hepatitis B immunization, and many other approaches (e.g., early detection and treatment of otherSTIs to reduce the efficiency of sexual

transmission of HIV); and (3) shortening of the duration of infectivity of STDs through early detection and curative or suppressive treatment of patients and their sexual partners.

Primary care physicians usually do not screen for illicit drug use or sexual risk behaviors, even when typical patients have classic presentations for HIV infection or anotherSTD. In fact, clinicians often focus only on detection and treatment of curable STDs to reduce the duration of infectivity. They generally have relatively little training or experience in risk assessment, counseling on risk reduction, tracing and treatment of sexual contacts, or condom promotion. Financial and time constraints imposed by managed-care practice patterns may further curtail screening and prevention services. As outlined inFig. 132-3, the efforts of clinicians simply to detect and treat STDs depend in part on societal efforts to teach young people how to recognize symptoms of STDs; to motivate those with symptoms to seek care promptly; and to make such care accessible, affordable, and acceptable, especially to the young indigent patients most likely to acquire an STD.

Since many infected individuals develop no symptoms or fail to recognize and report symptoms, clinicians should routinely perform anSTI risk assessment for teenagers and young adults as a selective screen. U.S. Preventive Services Task Force Guidelines recommend screening sexually active females£25 years of age for *C. trachomatis* whenever they present for health care (at least once a year); older women should be tested if they have more than one sexual partner, have begun a new sexual relationship since the previous test, or have anotherSTDdiagnosed. In the United States, widespread selective screening of young women for cervical *C. trachomatis* infection in some regions has been associated with a 50 to 60% drop in prevalence, and such screening also protects the individual woman fromPID. Sensitive urine-based genetic amplification tests permit expansion of screening to men and teenage boys and to women in settings where a pelvic examination is not planned or is impractical.

Although gonorrhea is now substantially less common than chlamydial infection in industrialized countries, screening tests for *N. gonorrhoeae* are still appropriate for women and teenage girls attendingSTDclinics and for sexually active teens and young women from areas of high gonorrhea prevalence. Routine screening of asymptomatic men for urethral gonorrhea has a very low yield in the primary care setting. However, genetic amplification tests that combine screening for *N. gonorrhoeae* and *C. trachomatis* in a single low-cost assay may facilitate the prevention and control of both infections in populations at high risk.

All patients with newly detectedSTIs or at high risk for STIs according to routine risk assessment as well as all pregnant women should be encouraged to undergo serologic testing for syphilis and HIV infection, with appropriate HIV counseling before and after testing. Several randomized trials have shown that *risk reduction counseling* of patients with STDs significantly lowers subsequent risk of acquiring an STD. Preimmunization serologic testing for antibody toHBV is indicated for unvaccinated persons who are known to be at high risk, such as homosexually active men and injection drug users. In most young persons, however, it is more cost-effective to vaccinate against HBV without serologic screening.

*Partner notification* is the process of identifying and informing partners of infected patients of possible exposure to anSTI and of examining, testing, and treating partners as appropriate. In a recently summarized series of 22 reports concerning partner notification during the 1990s, index patients with gonorrhea or chlamydial infection named a mean of 0.75 to 1.6 partners, of whom one-fourth to one- third were infected; those with syphilis named 1.8 to 6.3 partners, with one-third to one-half infected; and those with HIV infection named 0.76 to 5.31 partners, with up to one-fourth infected. Persons who transmit infection or who have recently been infected and are still in the incubation period usually have no symptoms or only mild symptoms and seek medical attention only when notified of their exposure. Therefore, the clinician must encourage patients to participate in partner notification, ensure that exposed persons are notified, and guarantee confidentiality to all involved. In the United States, local health departments will usually offer assistance in partner notification, treatment, and/or counseling. It seems both feasible and most useful to notify those partners exposed within the patient's likely period of infectiousness, which is often considered the preceding 1 month for gonorrhea, 1 to 2 months for chlamydial infection, and up to 3 months for early syphilis.

Persons with a new-onsetSTDalways have a *source* contact who gave them the infection; in addition, they may have a *secondary* (*spread* or *exposed*) contact with whom they had sex after becoming infected. The identification and treatment of these two types of contacts have different objectives. Treatment of the source contact (often a casual contact) benefits the community by preventing further transmission; treatment of the recently exposed secondary contact (typically a spouse or another steady sexual partner) prevents both the development of serious complications (such asPID) in the partner and reinfection of the index patient.

In summary, clinicians and public health agencies share responsibility for the prevention and control ofSTDs. In the managed-care era, the role of primary care clinicians has become increasingly important in prevention as well as in diagnosis and treatment.

(Bibliography omitted in Palm version)

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Back to Table of Contents

# 133. PELVIC INFLAMMATORY DISEASE - *King K. Holmes*, *Robert C. Brunham*

## DEFINITION

The term *pelvic inflammatory disease* (PID) usually refers to infection that ascends from the cervix or vagina to involve the endometrium and/or fallopian tubes. Infection can extend beyond the reproductive tract to cause pelvic peritonitis, generalized peritonitis, perihepatitis, or pelvic abscess. In rare instances, infection extends secondarily to the pelvic organs from adjacent foci of inflammation (e.g., sites of appendicitis, regional ileitis, or diverticulitis), as a result of hematogenous dissemination (e.g., of tuberculosis), or as a rare complication of certain tropical diseases (e.g., schistosomiasis). Intrauterine infection can be primary (spontaneously occurring and usually sexually transmitted) or secondary to invasive intrauterine surgical procedures (e.g., dilatation and curettage, termination of pregnancy, insertion of an intrauterine device, or hysterosalpingography) or to parturition. Endometritis or endomyometritis is particularly common following delivery by emergency cesarean section when antibiotic prophylaxis is not used.

PIDis uncommon during pregnancy itself. The uterotubal junction is closed as early as the seventh week of pregnancy, and the chorioamnion becomes approximated to the endocervical os, sealing off the intrauterine cavity, at the twelfth to fifteenth week of gestation. As a consequence, ascending intrauterine infection prior to the twelfth week of gestation may be associated (as either cause or effect) with endometritis and spontaneous abortion, while ascending infection after the twelfth week may be associated with chorioamnionitis.

Spontaneously occurringPID can be of the chronic or the acute type. Chronic PID due to *Mycobacterium tuberculosis* has become uncommon in industrialized countries. However, subacute or chronic PID caused by persistent or repeated infection with *Chlamydia trachomatis* is thought to be common.

Although the clinical diagnosis ofPID is imprecise, the use of endometrial biopsy together with laparoscopy provides objective evidence of a continuum progressing from cervicitis alone to endometritis, to salpingitis, and to peritonitis. In this chapter, *PID* is used to refer to the clinical syndrome that includes these conditions, while the term *salpingitis* is restricted to cases of visually or histopathologically confirmed inflammation of the fallopian tubes. The distinction between endometritis and salpingitis may be important, because long-term sequelae are much more common after salpingitis. These sequelae include infertility due to bilateral tubal occlusion, peritubal adhesions, ectopic pregnancy due to tubal damage without occlusion, chronic pelvic pain, and recurrent PID.

## ETIOLOGY

The etiology ofPID has varied greatly among studies for reasons related to the selection of patients, the prevalence of sexually transmitted disease (STD) pathogens at the time and place of the study, and methodology. As is summarized inTable 133-1, the agents most often implicated in acute PID include those that are primary causes of cervicitis (*Neisseria gonorrhoeae* and *C. trachomatis*) and those that can be regarded as components of an altered vaginal flora.

During the 1980s, *N. gonorrhoeae* and/or *C. trachomatis* was found in 65% of women with a clinical diagnosis ofPID at San Francisco General Hospital and in 85% of patients with proven salpingitis and endometritis in Seattle; in both studies, gonorrhea was nearly twice as common as chlamydial infection and dual infection was common. However, in Western Europe and parts of the United States, as gonococcal infection has come under much better control, endocervical gonococcal infection has been found in a declining proportion of women with PID, and the microbial etiology cannot be defined in a substantial proportion of cases. In general, PID is most often associated with gonorrhea where there is a high incidence of gonorrhea -- e.g., in developing countries and in indigent, inner-city populations in the United States. In several studies of women with PID, up to two-thirds of women with endocervical cultures positive for *N. gonorrhoeae* have also had endometrial, peritoneal, or tubal cultures positive for this organism. Similarly, studies of women with proven PID have shown that *C. trachomatis* can be demonstrated by culture or immunofluorescent staining in the endometrium or tubes of the majority of those who have endocervical chlamydial infection.

Anaerobic and facultative anaerobic organisms (especially *Prevotella* species, peptostreptococci, *Escherichia coli*, and group B streptococci) and genital mycoplasmas have been isolated from specimens obtained at laparoscopy from the peritoneal fluid or fallopian tubes in a varying proportion -- typically one-fourth to one-third -- of women withPIDstudied in the United States. These vaginal organisms can be found in association with chlamydial or gonococcal infection as well as in the absence of such infection. The importance of vaginal organisms in salpingitis has probably been overestimated in some studies in which specimens were obtained for cultures by culdocentesis or endometrial aspiration, procedures in which contamination of the aspirated specimen by vaginal flora is possible. However, specimens obtained by laparoscopy from some patients with PID have also contained anaerobic and facultative species. A compilation of seven studies of the microbial etiology of PID showed that 5 to 78% of patients had anaerobes and facultative bacteria isolated from the upper genital tract. It is extremely difficult to determine the exact microbial etiology of an individual case of PID because of the frequency of mixed infection, the difficulty in sampling the fallopian tube itself, and the complexity of the microbiologic techniques required to detect the various fastidious pathogens involved. This situation has implications for the approach to empirical antimicrobial treatment of PID.

In general, first episodes of acutePID are particularly likely to be caused by *N. gonorrhoeae* and/or *C. trachomatis*. These sexually transmitted pathogens are implicated somewhat less often in recurrent bouts of acute PID, in episodes occurring in women with intrauterine devices (IUDs), in episodes precipitated by invasive intrauterine diagnostic or therapeutic procedures (which are often associated with ascending infection caused by endogenous vaginal flora), and perhaps in HIV-associated PID.

**EPIDEMIOLOGY**

It has been estimated that about 850,000 cases ofPIDoccurred in the United States each year during the mid-1970s. PID is not a reportable disease in the United States; surveillance of physicians in private practice and of hospital discharges suggests that the incidence of PID increased from the mid-1960s through the mid-1970s and may

then have decreased. Hospitalization for acute PID declined steadily from 1982 through 1997, and initial visits to physicians' offices for PID have been declining since the mid-1980s. Furthermore, the number of hospitalizations for ectopic pregnancy in the United States fell by about two-thirds from 1989 to 1997.

AcutePID is almost exclusively a disease of sexually active women. Important risk factors include a history of salpingitis or of recent vaginal douching; the use of anIUD, particularly the Dalkon shield, has also been a risk factor. In most studies, the relative risk of PID among IUD users is higher in nulliparous than in parous women and is greatest during the first few months after IUD insertion. The increased risk of PID among IUD users is evident mainly among those with multiple sex partners. In contrast, women using oral contraceptives appear to be at decreased risk of PID. Barrier methods of contraception also make PID less likely by reducing the risk of chlamydial and gonococcal infection. Tubal sterilization reduces (but does not completely eliminate) the risk of salpingitis by preventing intraluminal spread of infection into the tubes.

**PATHOGENESIS**

Factors cited as possibly contributing to the upward spread of gonococci and chlamydiae from the endocervix to the endometrium and endosalpinx include estrogen-dominated (thin) cervical mucus, attachment to sperm that migrate upward into the tubes, use of anIUD, vaginal douching, menstruation, and subendometrial myometrial contractions, which move particulate matter from the cervix to the fundus of the uterus between days 5 and 14 of the menstrual cycle. It is important that the onset of symptoms of *N. gonorrhoeae*-associated and *C. trachomatis*-associatedPIDoften occurs during or soon after the menstrual period. In fallopian tube organ cultures in vitro, gonococci attach to the surface of the secretory columnar cells (but not the ciliated cells) of the endosalpinx. Gonococcal pili and perhaps other surface proteins are important in this attachment. Gonococci are then taken into the secretory cells by endocytosis. They pass through the cells -- and perhaps between cells -- and are extruded through the base of the cell into the submucosal connective tissue. Ciliary motion ceases, and then ciliated cells, although not directly invaded by gonococci, are sloughed from the mucosa -- a factor that may render the tubes more susceptible to superinfection by other organisms. It is uncertain whether this loss of ciliated cells is irreversible in vivo. Gonococcal endotoxin and peptidoglycan as well as certain cytokines (such as tumor necrosis factora) appear to be responsible for these cytotoxic effects.

*C. trachomatis* also infects the columnar cells of the fallopian tube but produces little damage in tubal organ cultures, perhaps because the host response is more important than directly toxic effects of bacterial products in the pathogenesis of chlamydial salpingitis. *Chlamydia*-infected epithelial cells secrete a number of proinflammatory cytokines, which are chemotactic for neutrophils and mononuclear cells. Routine endometrial biopsies from women with chlamydial mucopurulent cervicitis (MPC) show endometritis in approximately one-half of cases. Endometritis detected in this way is sometimes but not always associated with symptoms of severe abdominal pain, presentation during days 1 through 7 of the menstrual cycle, signs of uterine tenderness, and an erythrocyte sedimentation rate (ESR) of ³20 mm/h. Adnexal tenderness, cervical motion tenderness, and rebound tenderness as well as leukocytosis and elevated C-reactive protein levels are all more common in women with

laparoscopic evidence of salpingitis than in those with endometritis alone. Chlamydial inclusions are demonstrable by direct immunofluorescence in columnar epithelial cells of the endometrium and endosalpinx. The endometrial biopsies usually show neutrophils infiltrating the epithelium and plasma cells infiltrating the stroma, findings also seen in gonococcal endometritis but not in the uninfected endometrium. Experimental inoculation of the fallopian tubes of lower primates with *C. trachomatis* has shown that repeated exposure to *C. trachomatis* leads to the greatest degree of tissue inflammation and damage; this finding suggests that immunopathology also underlies the pathogenesis of chlamydial disease.

The pathogenesis ofPIDattributable to mycoplasmas or other vaginal anaerobic or facultative organisms is less well studied. It is possible that other vaginal organisms implicated in PID often cause tubal infection in women whose tubes have already been damaged by a primary sexually transmitted pathogen (i.e., *N. gonorrhoeae* or *C. trachomatis*). The vaginal organisms implicated in PID are found in the vagina most often and in greatest concentration in bacterial vaginosis, and there is epidemiologic evidence that bacterial vaginosis itself is a predisposing factor for PID (just as poor oral hygiene is a risk factor for aspiration pneumonia).

Certain other iatrogenic factors, such as dilatation and curettage or cesarean section, can increase the risk ofPID in women with endocervical gonococcal or chlamydial infection. Evidence indicates that among women undergoing cesarean section, the presence of bacterial vaginosis increases the risk of postpartum endometritis.

## CLINICAL MANIFESTATIONS

**Tuberculous Salpingitis** Unlike nontuberculous salpingitis, genital tuberculosis often occurs in older women, many of whom are postmenopausal. Presenting symptoms include abnormal vaginal bleeding, pain (including dysmenorrhea), and infertility. Bimanual pelvic examination may be normal, though about one-quarter of these women have had adnexal masses. Endometrial biopsy shows tuberculous granulomas and provides optimal specimens for culture.

**Nontuberculous Salpingitis** Symptoms of nontuberculous salpingitis classically evolve from a yellow or malodorous vaginal discharge caused byMPCand/or bacterial vaginosis to midline abdominal pain and abnormal vaginal bleeding caused by endometritis and then to bilateral lower abdominal and pelvic pain caused by salpingitis, with nausea and vomiting and increased abdominal tenderness caused by peritonitis. Some patients have diffuse abdominal pain caused by generalized peritonitis or pleuritic right upper quadrant pain caused by perihepatitis. The pattern in which symptoms evolve varies from patient to patient and is also related to the etiology of thePID.

The onset ofIUD-associatedPID is typically gradual and may be preceded by the malodorous vaginal discharge characteristic of bacterial vaginosis. The onset of gonococcal PID may be more acute than that of chlamydial PID, and PID of either etiology usually presents during the first half of the menstrual cycle.

The abdominal pain in nontuberculous salpingitis is usually described as dull or aching. In some cases, pain is lacking or is atypical, and active inflammatory changes are found

in the course of an unrelated evaluation or procedure, such as a tubal ligation or a laparoscopic evaluation for infertility. Abnormal uterine bleeding precedes or coincides with the onset of pain in ~40% of women withPID, symptoms of urethritis (dysuria) occur in 20%, and symptoms of proctitis (anorectal pain, tenesmus, and rectal discharge or bleeding) are occasionally seen in women with gonococcal or chlamydial infection.

Speculum examination shows evidence of MPC(yellow endocervical discharge, easily induced endocervical bleeding) in the majority of women with gonococcal or chlamydialPID. Cervical motion tenderness is produced by stretching of the adnexal attachments on the side toward which the cervix is pushed. Bimanual examination reveals uterine fundal tenderness due to endometritis and abnormal adnexal tenderness due to salpingitis that is usually, but not necessarily, bilateral. Adnexal swelling is palpable in about one-half of women with acute salpingitis, but evaluation of the adnexae in a patient with marked tenderness -- even by an experienced examiner -- is not reliable. The initial temperature is >38°C in only about one-third of patients with acute salpingitis; thus fever is not required for the diagnosis. Laboratory findings include elevation of theESR in 75% of patients with acute salpingitis and elevation of the peripheral white blood cell count in up to 60%.

Certain clinical manifestations of acutePID have been correlated with microbial etiology. For example, the onset of salpingitis is related to menses in women with gonococcal or chlamydial infection. Women with *N. gonorrhoeae*- or *C. trachomatis*-associated salpingitis are significantly younger than women with salpingitis of other etiologies. In a Swedish study, women with *Chlamydia*-associated salpingitis had more indolent disease, with mild symptoms of significantly longer duration and less fever, than women with gonorrhea-associated salpingitis. Women with polymicrobial PID more often have tubal or pelvic abscess formation. It is suspected that, for all recognized cases of symptomatic acute chlamydial salpingitis, there is a comparable number of unrecognized cases of indolent or mildly symptomatic chlamydial salpingitis. Furthermore, it is thought that subclinical chronic or recurrent chlamydial salpingitis may be a major cause of female infertility.

**Perihepatitis and Periappendicitis** Symptoms of perihepatitis, including pleuritic upper abdominal pain and tenderness (usually localized to the right upper quadrant), develop in 3 to 10% of women with acutePID. The onset of symptoms of perihepatitis takes place during or after the onset of symptoms of PID and may overshadow lower abdominal symptoms, thereby leading to a mistaken diagnosis of cholecystitis. In perhaps 5% of cases of acute salpingitis, early laparoscopy reveals inflammation ranging from edema and erythema of the liver capsule to exudate with fibrinous adhesions between the visceral and parietal peritoneum. When treatment is delayed and laparoscopy is performed late, dense "violin-string" adhesions are seen over the liver; chronic exertional or positional right upper quadrant pain ensues when traction is placed on the adhesions. Although perihepatitis, also known as the *Fitz-Hugh-Curtis syndrome*, was for many years specifically attributed to gonococcal PID, most cases are now attributed to chlamydial salpingitis. In patients with chlamydial salpingitis, serum titers of microimmunofluorescent antibody to *C. trachomatis* are typically much higher when perihepatitis is present than when it is absent, and it has been suggested that repeated chlamydial infections are responsible for perihepatitis.

Physical findings include right upper quadrant tenderness and usually include adnexal tenderness and cervicitis, even in patients whose symptoms are not suggestive of salpingitis. Liver function tests are nearly always normal, since inflammation is largely limited to the liver capsule and usually spares the parenchyma. Ultrasonography of the right upper quadrant is normal. The presence ofMPC and pelvic tenderness in a young woman with subacute pleuritic right upper quadrant pain and normal ultrasonography of the gallbladder points to a diagnosis of perihepatitis.

Periappendicitis (appendiceal serositis without involvement of the intestinal mucosa) has been found in ~5% of patients undergoing appendectomy for suspected appendicitis and can occur as a complication of gonococcal or chlamydial salpingitis.

**Influence of HIV Infection** HIV infection with immunosuppression increases the risk of repeated gonococcal and chlamydial infections among repeatedly exposed female sex workers, presumably by attenuating the immune response to repeated infection. Further, among women who acquire gonococcal or chlamydial infection of the cervix, HIV infection with immunosuppression increases the likelihood of developing clinical manifestations of salpingitis. Finally, among women with salpingitis, HIV infection is associated with increased severity of salpingitis and with tuboovarian abscess requiring hospitalization and surgical drainage. However, among African women with confirmedPID, those with HIV infection appear less likely to have gonorrhea or chlamydial infection than those without HIV infection, a difference suggesting that other etiologies are especially important in the immunosuppressed patient. Nonetheless, among women with HIV infection and salpingitis, the clinical reponse to conventional antimicrobial therapy (coupled with drainage of tuboovarian abscess, when found) has been satisfactory.

## DIAGNOSIS

Early diagnosis and initiation of therapy are essential to minimize tubal scarring. A reanalysis of Westrom's cohort of Swedish women with proven salpingitis showed that those who delayed seeking care were three times more likely than those who sought care promptly to experience subsequent infertility or ectopic pregnancy. Appropriate treatment must not be withheld from patients who have an equivocal diagnosis; it is better to err on the side of overdiagnosis and overtreatment. On the other hand, it is essential to differentiate between salpingitis and other pelvic pathology, particularly surgical emergencies such as appendicitis and ectopic pregnancy.

No readily available clinical finding or laboratory test, short of laparoscopy, definitively identifies salpingitis, and routine laparoscopy to confirm suspected salpingitis is generally impractical. Most patients with acutePID have lower abdominal pain of <3 weeks' duration, pelvic tenderness on bimanual pelvic examination, and evidence of lower genital tract infection (e.g.,MPC). Approximately 60% of such patients have salpingitis at laparoscopy. Among the patients with these findings, a rectal temperature>38°C, a palpable adnexal mass, and elevation of theESR over 15 mm/h also raise the probability of salpingitis, which has been found at laparoscopy in 68% of patients with one of these additional findings, 90% of patients with two, and 96% of patients with three. However, only 17% of all patients with laparoscopy-confirmed salpingitis have had all three additional findings.

MPCis probably responsible for the presence of neutrophils in vaginal fluid inPID. In a woman with pelvic pain and tenderness, demonstration of an increased number of neutrophils (30 per 1000´ microscopic field in strands of cervical mucus) increases the predictive value of a clinical diagnosis of acute PID.

Several clinical features other than the presence of cervicitis also favor the diagnosis of acutePID. These include onset with menses, history of recent abnormal menstrual bleeding, presence of anIUD, history of salpingitis, and sexual exposure to a male with urethritis. Detection of polymorphonuclear leukocytes in pelvic peritoneal fluid aspirated by culdocentesis supports a diagnosis of suspected salpingitis. Urethritis or proctitis may occur in chlamydial or gonococcal infection but may also represent a urinary tract source or an intestinal source, respectively. Appendicitis or another disorder of the gut is favored by the early onset of anorexia, nausea, or vomiting; the onset of pain later than day 14 of the menstrual cycle; or unilateral pain limited to the right or left lower quadrant. All women in whom the diagnosis of PID is being considered should be evaluated for ectopic pregnancy. The more sensitive serum assays for humanb-chorionic gonadotropin are usually positive when ectopic pregnancy is the diagnosis. Ultrasonography and magnetic resonance imaging (MRI) can be useful for the identification of tuboovarian or pelvic abscess. MRI or intravaginal ultrasound assessment of the tubes has been reported to show increased tubal diameter, intratubal fluid, or tubal wall thickening in cases of salpingitis.

Laparoscopy is the most specific method for diagnosis of acute salpingitis. Although laparoscopic findings may be normal if inflammation is limited to the endosalpinx or the endometrium, patients with suspectedPID who have a normal laparoscopy have a better prognosis (with no sequelae at all or fewer sequelae) than patients who have abnormal laparoscopic findings. The primary and uncontested value of laparoscopy in women with lower abdominal pain is for the exclusion of other surgical problems. Some of the most common or serious problems that may be confused with salpingitis (e.g., acute appendicitis, ectopic pregnancy, corpus luteum bleeding, ovarian tumor) are unilateral. Unilateral pain or pelvic mass, though not incompatible with PID, is a strong indication for laparoscopy unless the clinical picture warrants laparotomy instead. Atypical clinical findings, such as the absence of lower genital tract infection, a missed menstrual period, a positive pregnancy test, or failure to respond to appropriate therapy, are other frequent indications for laparoscopy.

Laparoscopic criteria used for the diagnosis of salpingitis include (1) erythema of the fallopian tube, (2) edema of the fallopian tube, and (3) seropurulent exudate or fresh, easily lysed adhesions at the fimbriated end or on the serosal surface of a fallopian tube.

Endometrial biopsy is relatively sensitive and specific for the diagnosis of endometritis when the endometrial changes described above are found, and the presence of endometritis correlates well with the presence of salpingitis. Endometritis is found in at least three-fourths of women with laparoscopically confirmed salpingitis and is not found in women withoutPID.

The etiologic diagnosis ofPID can be further studied by culture or other testing of

specimens obtained by endocervical swab, endometrial aspiration, or culdocentesis or by laparoscopy or laparotomy. Endocervical swab specimens should be examined by Gram's staining for neutrophils and gram-negative diplococci and by culture or DNA amplification test for *N. gonorrhoeae*. Compared with culture, the sensitivity of Gram's staining is ~60% and the specificity is >95%. The endocervical swab specimen should also be tested for *C. trachomatis* by culture or amplification assays for chlamydial DNA or RNA. Although detection of either *N. gonorrhoeae* or *C. trachomatis* in the endocervix does not prove that either agent is also present in the upper genital tract, this finding strongly supports the diagnosis of PID. The clinical diagnosis of PID made by expert gynecologists is confirmed by laparoscopy or endometrial biopsy in only ~60% of patients but in ~90% of those who also have cultures positive for *N. gonorrhoeae* or *C. trachomatis*. There is no evidence that the isolation of anaerobes or facultative aerobes from the cervix or vagina correlates with the presence of these organisms in the upper genital tract in acute PID, but this point has not been well studied. In one study, the isolation of *Haemophilus influenzae* from the endocervix was highly correlated with this organism's recovery from the fallopian tube in cases of salpingitis. Despite the risk of contamination of endometrial specimens with components of the vaginal flora, one study showed a 2.6-fold increase in the rate of recovery of anaerobic gram-negative rods (especially *Prevotella*, black-pigmented rods, and *Fusobacterium*) by endometrial biopsy in women with endometritis compared with control women. When laparoscopy is performed, material can be obtained directly from the cul-de-sac or the fimbriated opening of the tube or by tubal aspiration if pyosalpinx is present. Such specimens should be cultured for anaerobic and facultative pathogens as well as for *N. gonorrhoeae* and *C. trachomatis*.

## TREATMENT

Women with PIDcan be treated as either outpatients or inpatients. Over the past decade, the costs of PID treatment have declined considerably because of the increased management of patients in the ambulatory setting, with use of highly active, well-absorbed antimicrobial agents. Nonetheless, hospitalization may be necessary and should be considered when (1) the diagnosis is uncertain and surgical emergencies such as appendicitis and ectopic pregnancy cannot be excluded, (2) pelvic abscess is suspected, (3) severe illness or nausea and vomiting preclude outpatient management, (4) the patient has HIV infection, (5) the patient is assessed as unable to follow or tolerate an outpatient regimen, or (6) the patient has failed to respond to outpatient therapy. If outpatient treatment is embarked on, clinical follow-up after 48 to 72 h of antibiotic treatment should be arranged. Treatment should cover *N. gonorrhoeae*, *C. trachomatis*, gram-negative facultative bacteria (especially *E. coli* and *H. influenzae*), vaginal anaerobes, and group B streptococci. Several antimicrobial combinations do provide a broad spectrum of activity against the major pathogens in vitro, but many have not been adequately evaluated for clinical efficacy in PID (Table 133-2).

**Examples of Combination Regimens with Broad Activity Against Major Pathogens in PID** Recommended combination regimens for ambulatory or parenteral management of PID are presented in Table 133-3.

Women managed as outpatients should receive a combined regimen with broad activity, such as ceftriaxone [250 mg intramuscularly (IM)] followed by doxycycline (100 mg by

mouth, twice a day for 14 days). Metronidazole (500 mg by mouth twice daily) can be added, if tolerated, to enhance activity against anaerobes. Alternatively, ofloxacin (400 mg twice daily) plus metronidazole (500 mg twice daily), both continued for 14 days, provide good coverage of the major pathogens.

The following two parenteral regimens have given nearly identical results in a multicenter randomized trial:

1. Doxycycline [100 mg twice a day, given intravenously (IV) or orally] plus cefotetan (2.0 g IV every 12 h) or cefoxitin (2.0 g IV every 6 h). These drugs should be continued by the IV route for at least 48 h after the patient's condition improves, then followed with doxycycline (100 mg by mouth, twice a day) to complete 14 days of therapy.

2. Clindamycin (900 mg IV every 8 h) plus gentamicin (2.0 mg/kg IV or IM followed by 1.5 mg/kg every 8 h) in patients with normal renal function. Once-daily dosing of gentamicin (with combination of the total daily dose into a single daily dose) has not been evaluated inPID but has been efficacious in other serious infections and could be substituted. Treatment with these drugs should be continued for at least 48 h after the patient's condition improves, then followed with doxycycline (100 mg orally twice a day) or with clindamycin (450 mg orally four times a day) to complete 14 days of therapy. In cases with tuboovarian abscess, many experts use oral clindamycin rather than doxycycline for continued therapy to provide better coverage for anaerobic infection.

**Management of Sexual Partners** Sexual partners of patients with acutePID -- particularly those who have been partners within the 1 to 2 months before the onset of symptoms of PID -- should be examined forSTDs and promptly treated with a regimen effective against uncomplicated gonococcal and chlamydial infection. An important point is that³50% of the sexual partners of women with gonococcal and/or chlamydial PID have subclinical urethral infection and may be unaware of their infection status. Treatment of PID should be considered inadequate until sexual partners have been properly evaluated and treated.

**Follow-Up** Hospitalized patients should show substantial clinical improvement within 3 to 5 days. Women treated as outpatients should be clinically reevaluated within 72 h. A follow-up telephone survey of women seen in an emergency room and given a prescription for 10 days of oral doxycycline forPIDfound that 28% never filled the prescription and 41% stopped taking medication early (after an average of 4.1 days), often because of persistent symptoms, lack of symptoms, or side effects. Women not responding favorably to ambulatory therapy should be hospitalized. After completion of treatment, tests for persistent or recurrent infection with *N. gonorrhoeae* or *C. trachomatis* should be performed if symptoms persist or recur or if the patient has not complied with therapy or has been reexposed to an untreated sex partner.

**Removal of anIUD**Although a beneficial impact of IUD removal on the response of acute salpingitis to antimicrobial therapy and on the risk of recurrent salpingitis has not been proven, removal of the IUD 2 or 3 days after the initiation of antimicrobial therapy seems reasonable. When an IUD is removed, contraceptive counseling is essential.

**Surgery** Surgery is necessary for the treatment of salpingitis only in the face of

life-threatening infection (such as rupture or threatened rupture of a tuboovarian abscess) or for drainage of an abscess. Ultrasonography andMRI are useful for diagnosing and monitoring pelvic abscesses. Conservative surgical procedures are usually sufficient. Pelvic abscesses can often be drained by posterior colpotomy, and peritoneal lavage can be used if there is generalized peritonitis.

## PROGNOSIS

Among 900 women who underwent long-term follow-up for a mean period of 8 years after successful treatment of an acute episode ofPID with various regimens in Sweden, late sequelae included infertility due to bilateral tubal occlusion, ectopic pregnancy due to tubal scarring without occlusion, chronic pelvic pain, and recurrent salpingitis. Chronic pain lasting>6 months was seen in 18% of patients, and infertility due to tubal occlusion in 17%; 4% of the pregnancies that did occur were ectopic, representing approximately a sixfold increase over the expected rate of ectopic pregnancies. The rate of infertility after salpingitis was found to be related to the age of the patient, the duration of symptoms when treatment was started, the severity of salpingitis (as determined by laparoscopy) at the time of diagnosis, and the number of episodes of salpingitis. The postsalpingitis risk of infertility due to tubal occlusion among sexually active women not using contraceptives was 14% at 15 to 24 years of age and 26% at 25 to 34 years of age; the risk for women of all ages combined was 11% after one episode of salpingitis, 23% after two episodes, and 54% after three or more episodes. Women with chlamydial salpingitis who developed more severe inflammatory damage to the reproductive tract had significantly increased titers of antibody to the chlamydial heat-shock protein HSP60, as did women with infertility or ectopic pregnancy following chlamydial salpingitis. The risk of infertility after treated gonococcal salpingitis appeared lower than that after chlamydial salpingitis or polymicrobial PID. A study of outcomes of PID at the University of Washington found a sevenfold increase in the risk of ectopic pregnancy and an eightfold increase in the rate of hysterectomy after PID.

In several countries, a striking relationship has also been found between infertility due to tubal occlusion and the prevalence and titer of antibody to *C. trachomatis*. Recurrent salpingitis has been seen in ~15 to 25% of women treated for salpingitis in various studies.

## PREVENTION

Prevention of PIDdepends first on the effective control of gonococcal and chlamydial infection in the general population. Effective methods include the promotion of changes in sexual behavior and the use of barrier contraceptives together with ensuring ready access to modern methods of diagnosis of these infections and effective treatment of sex partners to control further spread. The decline in popularity of the IUD, particularly among nulliparous women, has undoubtedly helped to reduce the incidence of PID. It is also possible, but not proven, that the use of oral contraceptives and the declining proportion of women who have practiced vaginal douching since the link between douching and PID became known have contributed to lower rates of PID. A randomized controlled trial designed to determine whether selective screening for chlamydial infection reduced the risk of subsequent PID showed that women randomized to undergo screening had a 56% lower rate of PID over the following year than did women

receiving the usual care without screening. This report strongly supports risk-based screening for *Chlamydia* as a highly effective way to reduce the incidence of PID and the prevalence of post-PID sequelae.

The complications and sequelae of salpingitis are minimized by early diagnosis and prompt effective treatment. It seems logical, but is unproven, that broad-spectrum therapy effective against all of the common causes ofPIDoffers the best outcome. Although few methodologically sound clinical trials (especially with prolonged follow-up) have been conducted, one meta-analysis showed a benefit of providing good coverage against anaerobes. One placebo-controlled study showed that concurrent anti-inflammatory therapy with prednisolone hastened the reduction of acute inflammatory changes but did not improve the end results, as measured by fertility, hysterosalpingographic findings, or chronic pain. The potential value of anti-inflammatory therapy remains to be evaluated adequately.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 3 -CLINICAL SYNDROMES: NOSOCOMIAL INFECTIONS

# 134. INFECTION CONTROL IN THE HOSPITAL - *Robert A. Weinstein*

The costs of nosocomial (hospital-acquired) infections are great. It is estimated that nosocomial infections cost $4.5 billion and contribute to 88,000 deaths annually. Although infection-control and hospital epidemiology activities have been the subjects of increasing scientific study over the past 30 years, efforts to lower infection risks have been continually challenged by the growing numbers of immunocompromised patients, antibiotic-resistant bacteria, fungal and viral superinfections, and invasive devices and procedures. Four international decennial conferences on infection control, organized by the Centers for Disease Control and Prevention (CDC), have clearly documented these formidable trends. This chapter reviews the basic surveillance and prevention activities that have been developed to deal with these problems and that form the foundation for current hospital epidemiology programs.

## ORGANIZATION AND RESPONSIBILITIES OF INFECTION-CONTROL PROGRAMS

The standards of the Joint Commission on Accreditation of Healthcare Organizations require all accredited hospitals to have an active program for surveillance, prevention, and control of nosocomial infections; a multidisciplinary infection-control committee usually oversees the program. The agents of the committee are the chairperson, who is preferably an infectious disease physician, and the infection-control practitioners, who are usually trained in nursing or medical technology and in epidemiology and public health. Education of physicians in infection control and hospital epidemiology is required in infectious disease fellowship programs and is available in courses provided by professional societies, primarily the Society for Healthcare Epidemiology of America.

In the 1970s, theCDC's extensive Study on the Efficacy of Nosocomial Infection Control found that nosocomial infection rates fell by 32% in hospitals that established programs with organized surveillance and control activities; a trained, effectual infection-control physician; and one infection-control practitioner per 250 beds. In contrast, rates in hospitals without effective programs increased by 18%. Since that study, the responsibilities and roles of hospital epidemiology programs have expanded in several directions. Diagnosis-related reimbursement has led hospital administrators to place increased emphasis on cost containment and on documentation of the cost-effectiveness of infection control. The quality-improvement movements and the Joint Commission have redirected infection-control attention, in part, beyond the mere writing of policies and procedures to improvement of the actual processes and optimization of outcomes. In a few hospitals, epidemiology programs have taken on additional pharmacoepidemiologic and antibiotic-use review responsibilities. Finally, all programs must now respond to increasing governmental regulation of hospital waste and to standards mandated by the Occupational Safety and Health Administration for protecting health care workers from occupational exposure to bloodborne pathogens and tuberculosis.

## SURVEILLANCE

Traditionally, infection-control practitioners survey inpatients for nosocomial infections

(defined as those neither present nor incubating at the time of admission). Surveillance involves a review of microbiology laboratory results, "shoe-leather" epidemiology on the nursing wards, application of standardized definitions of infection, ongoing dialogue with hospital workers, and common sense. Some innovative infection-control programs have taken advantage of the increased use of computerized pharmacy, microbiology, and other databases in hospitals to create algorithm-driven surveillance activities.

Most hospitals aim surveillance at infections that (1) are associated with a high level of morbidity, e.g., intensive care unit (ICU)-related infections and nosocomial pneumonia; (2) are costly, e.g., cardiac surgical wound infections; (3) are difficult to treat, e.g., infections due to antibiotic-resistant bacteria; (4) pose recurring epidemic problems, e.g., *Clostridium difficile*-related diarrhea; and (5) are potentially preventable, e.g., vascular access-related infections. Quality-assurance activities in infection control have led to increased surveillance of the compliance of personnel with infection-control policies (e.g., monitoring of actual adherence to hand-washing recommendations).

The results of surveillance are expressed as rates; for example, 5 to 10% of patients develop nosocomial infections. Although such overall statistics are often requested of hospitals by administrators or surveyors, they have little value unless qualified by site of infection, by patient population, and by exposure to risk factors. Meaningful denominators for infection rates include the number of patients exposed to a specific risk (e.g., rates of pneumonia among patients using mechanical ventilators) and the number of intervention days (e.g., rates of pneumonia per 1000 patient-days on a ventilator).

Temporal trends in rates should be reviewed, and rates should be compared with regional and national norms. However, even comparison rates generated by theCDC's ongoing National Nosocomial Infections Surveillance System, which collects data from more than 270 hospitals that use standardized definitions of nosocomial infections, have not been validated independently and represent a nonrandom sample of hospitals. Interhospital comparisons are easily confounded by the wide range in risk factors and in severity of underlying illnesses; unless rates are adjusted for these factors, comparisons may be misleading. Unfortunately, systems for making such adjustments either are rudimentary or have not been well validated.

The ongoing analysis of an individual hospital's infection rates helps to determine whether control efforts are succeeding and where increased education and control measures should be focused. Knowledge of infection rates is also useful in discussions with the hospital administration regarding areas to which additional resources should be directed.

## PREVENTION AND CONTROL MEASURES

**Epidemiologic Basis and General Measures** Nosocomial infections follow basic epidemiologic patterns that can help to direct prevention and control measures. Nosocomial pathogens have reservoirs, are transmitted by predictable routes, and require susceptible hosts. Reservoirs and sources exist in the inanimate environment (e.g., tap water contaminated with *Legionella*) and in the animate environment (e.g., infected or colonized health care workers, patients, and hospital visitors). The mode of

transmission most often is either cross-infection (e.g., indirect spread of pathogens from one patient to another on the inadequately washed hands of hospital personnel) or autoinoculation (e.g., aspiration of oropharyngeal flora into the lung along an endotracheal tube). Occasionally, pathogens (e.g., group A streptococci and many respiratory viruses) are spread indirectly from person to person via infectious droplets released by coughing or sneezing. Much less common -- but often devastating in terms of epidemic risk -- is true airborne spread of droplet nuclei (as in nosocomial chickenpox) or common-source spread by contaminated materials (e.g., iodophors contaminated with *Pseudomonas*). Factors that increase host susceptibility include underlying conditions and the many medical-surgical interventions and procedures that bypass or compromise normal host defenses.

Through its program, the hospital's infection-control committee must determine the general and specific measures used to control infections and must review and recommend specific antiseptics and disinfectants for hospital use. Given the prominence of cross-infection, hand washing is the single most important preventive measure in hospitals. Many studies have examined the antimicrobial activity of a wide variety of antiseptic-containing hand-washing agents. The use of such medicated agents is important before invasive procedures and possibly in ICU settings. In light of the poor general compliance with hand-washing recommendations, the importance of using any hand cleanser between patient contacts cannot be overemphasized (Table 134-1).

The fact that 25 to 50% of nosocomial infections are due to the combined effect of the patient's own flora and invasive devices highlights the importance of improvements in the use and design of such devices (Chap. 135). Intensive educational programs can be associated with at least a temporary reduction in infection rates through improved asepsis in handling and earlier removal of invasive devices, but the maintenance of such gains is often difficult. Epidemiologic studies are used increasingly to assess the value of newer devices and site-specific control measures and to debunk some traditional yet ineffective and costly measures, such as routine culturing of the environment and personnel for "pathogens."

**Urinary Tract Infections** Approaches to the prevention of urinary tract infections have included the use of topical meatal antimicrobials, drainage bag disinfectants, antimicrobial-coated catheters, and sealed catheter-drainage tube junctions to eliminate inadvertent breaks in the system. Because of conflicting study results, none of these measures is considered routine. Systemic antimicrobials given for other purposes decrease the risk of urinary tract infection during the first 4 days of catheterization, after which resistant bacteria or yeasts emerge as pathogens. Selective decontamination of the gut is also associated with a reduced risk. Again, however, neither approach is routine. Irrigation of catheters, with or without antimicrobials, may actually increase the risk of infection.

**Pneumonia** Control measures for pneumonia are aimed at the remediation of risk factors in general patient care (e.g., minimizing aspiration-prone supine positioning) and at meticulous aseptic care of respirator equipment (e.g., disinfecting or sterilizing all in-line reusable components such as nebulizers, replacing tubing circuits at intervals of >48 h -- rather than more frequently -- to lessen the number of breaks in the system,

and teaching aseptic technique for suctioning). In a large multicenter trial, sucralfate, which provides stress-ulcer prophylaxis without altering gastric pH, did not reduce the risk of ventilator-associated pneumonia, despite the theoretical advantage of lessened risk for gastric colonization by gram-negative bacilli. The benefit of selective decontamination of the oropharynx and gut with nonabsorbable antimicrobials has been controversial.

**Surgical Wound Infections** The most important control measures for surgical wound infections include the use of antimicrobial prophylaxis at the start of high-risk procedures, attention to technical surgical issues and operating-room asepsis (e.g., not shaving the operative site until surgery and avoiding open or prophylactic drains), and preoperative therapy for active infection. In one study, rates of postoperative infection were lower among patients who had normothermia maintained during colorectal surgery. Reporting of surveillance results to surgeons has been associated with reductions in infection rates. The increasingly extensive review of infection rates by regulatory agencies and third-party payers emphasizes the importance of stratifying rates by patient-related risk factors and of developing meaningful systems for interhospital comparisons and for wound surveillance after the patient's discharge from the hospital or clinic (when more than 50% of infections first become apparent).

**Infections Related to Vascular Access and Monitoring (See also Chap. 135)** Control measures for infections associated with vascular access and monitoring include the moving of peripheral or arterial catheters to a new site at specified intervals (e.g., every 72 h for peripheral intravenous catheters), which may be facilitated by use of an intravenous team; application of disposable transducers and aseptic technique for the accessing of transducers or other vascular ports; removal of "idle" catheters; and consideration of use of central venous catheters impregnated with anti-infective agents. Unresolved issues include the best frequency for the rotation of central venous catheter sites (guidewire-assisted catheter changes at the same site do not lessen infection risk); the best antiseptics for site preparation and for catheter dressing; the appropriate role for mupirocin ointment, a topical antibiotic with excellent antistaphylococcal activity, in site care; and the relative degrees of risk posed by percutaneous central catheters and by newer designs -- tunneled, totally implanted, or peripherally inserted central catheters (PICC lines). Improvements in composition of semitransparent access-site dressings and potential nursing benefits (ease of bathing and site inspection and protection of the site from secretions) favor use of such coverings.

**Isolation Techniques** Written policies for the isolation of infectious patients are a standard component of infection-control programs. In 1996, the CDC revised its isolation guidelines to be simpler; to recognize the importance of all body fluids, secretions, and excretions in the transmission of nosocomial pathogens; and to focus precautions on the major routes of infection transmission.

The revised guidelines contain two tiers of precautions. *Standard precautions* are designed for the care of all patients in hospitals to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources of infection. These precautions include gloving, as well as hand washing, for potential contact with blood; with all other body fluids, secretions, and excretions, regardless of whether they contain visible blood; with nonintact skin; and with mucous membranes. Depending on exposure

risks, standard precautions also include use of masks, eye protection, and gowns.

In the second tier are precautions for the care of patients with suspected or diagnosed colonization or infection with transmissible pathogens. These transmission-based guidelines collapse the older category- and disease-specific isolation guidelines into three sets of precautions based on probable routes of transmission: *airborne precautions*, *droplet precautions*, and *contact precautions*. Sets of precautions may be combined for diseases that have more than one route of transmission (e.g., varicella). Potentially contagious clinical syndromes, such as acute diarrhea, are included in the revised guidelines.

Because some prevalent antibiotic-resistant pathogens, particularly vancomycin-resistant enterococci (VRE), may be present on *intact* skin of patients in hospitals, some experts recommend gloving for all contact with patients who are acutely ill and/or from high-risk units, such asICUs. In recent trials, wearing gloves did not replace the need for hand washing because hands occasionally became contaminated during wearing or removal of gloves. Some studies have suggested that use of gowns and gloves compared with routine care of patients (i.e., using neither of these barriers) decreases the risk of nosocomial infection; however, more recent evaluation suggests that gowning by personnel does not add benefit beyond that conferred by gloving and hand washing. Nevertheless, requiring increased precaution levels can improve the compliance of health care workers with isolation recommendations by 30%.

## EPIDEMIC PROBLEMS

Outbreaks are always big news but probably account for fewer than 5% of nosocomial infections. The investigation and control of epidemics in hospitals require that infection-control personnel develop a case definition, confirm that an outbreak really exists (since many apparent epidemics are actually pseudo-outbreaks due to surveillance or laboratory artifacts), review aseptic practices and disinfectant use, determine the extent of the outbreak, perform an epidemiologic investigation to determine modes of transmission, work closely with microbiology personnel to culture for common sources or personnel carriers as appropriate and to type epidemiologically important isolates, and heighten surveillance to judge the effect of control measures. Control measures generally include the early reinforcement of routine aseptic practices during a search for compliance problems that may have fostered the outbreak, the ensuring of the appropriate isolation of cases (and the institution of cohort isolation and nursing if needed), and the implementation of further controls on the basis of the findings of the investigation. Examples of some potential epidemic problems follow.

**Chickenpox** When health care workers are exposed to chickenpox in the community or through patients with initially unrecognized infections, or when these employees work during the 24 h before developing chickenpox, infection-control practitioners institute a varicella exposure investigation and control plan. The names of exposed workers and patients are obtained; medical histories are reviewed, and (if necessary) serologic tests for immunity are conducted; physicians are notified of susceptible exposed patients; postexposure prophylaxis with varicella-zoster immune globulin (VZIG) is considered for immunocompromised or pregnant contacts (see Table 183-1); preemptive use of acyclovir is considered as an alternative strategy in some susceptible persons; and

susceptible exposed employees are furloughed during the at-risk period for disease (8 to 21 days, or 28 days if VZIG has been administered). Preexposure varicella vaccination can markedly decrease risk for susceptible employees.

**Tuberculosis** The resurgence of pulmonary tuberculosis in the United States since 1987 and a series of nosocomial outbreaks of infection with multidrug-resistant strains -- primarily involving patients with AIDS and their caregivers -- have led to a reevaluation of tuberculosis control. Important control measures include prompt recognition, isolation, and treatment of cases; recognition of atypical presentations (e.g., lower-lobe infiltrates without cavitation); use of negative pressure, 100% exhaust, private isolation rooms with closed doors, and six air changes per hour; use of face masks (approved by the National Institute for Occupational Safety and Health) by caregivers entering isolation rooms; possible use of high-efficiency particulate air filter units and/or ultraviolet lights for disinfecting air when other engineering controls are not feasible or reliable; and follow-up skin-testing of susceptible personnel who have been exposed to infectious patients before isolation.

**Group A Streptococci** The potential for a group A streptococcal outbreak should be considered when even a single nosocomial case occurs. Most outbreaks involve surgical wounds and are due to the presence of an asymptomatic carrier in the operating room. Investigation can be confounded by carriage at extrapharyngeal sites such as the rectum and vagina. Health care workers in whom carriage has been linked to nosocomial transmission of group A streptococci are removed from the patient-care setting and are not permitted to return until carriage has been eliminated by antimicrobial therapy.

***Aspergillus*** *Aspergillus* spores are common in the environment, particularly on dusty surfaces. When hospital ceiling tiles are removed to provide access for electrical wiring or plumbing or when dusty areas are disturbed during hospital renovation, the spores become airborne. Inhalation of spores by immunosuppressed (particularly neutropenic) patients creates a risk of pulmonary and/or paranasal sinus infection and disseminated aspergillosis. Routine surveillance among neutropenic patients for infections with filamentous fungi, such as *Aspergillus* and *Fusarium*, helps hospitals to determine whether they have unduly large environmental loads of these organisms. To lower the risk, hospitals should inspect and clean air-handling equipment on a routine schedule, review all planned hospital renovations with infection-control personnel and subsequently construct appropriate barriers, remove immunosuppressed patients from renovation sites, and consider the use of high-efficiency particulate air filters for rooms housing immunosuppressed patients.

***Legionella*** Sporadic and epidemic cases of nosocomial *Legionella* pneumonia are most often due to the contamination of potable water and predominantly affect immunosuppressed patients, particularly those receiving glucocorticoid medication. The risk varies greatly within and among geographic regions, depending on the extent of hospital hot-water contamination, on the presence or absence of high-risk patient populations, and on specific hospital practices (e.g., inappropriate use of nonsterile water in respiratory therapy equipment). Laboratory-based surveillance for nosocomial *Legionella* should be performed, and a diagnosis of legionellosis should probably be considered more often than it is. If cases are detected, environmental samples (e.g., tap

water) should be cultured. If cultures yield *Legionella* and if typing of clinical and environmental isolates reveals a correlation, eradication measures should be pursued (Chap. 151). An alternative approach is to periodically culture tap water on wards housing high-risk patients. If *Legionella* is found, a concerted effort should be made to culture samples from all patients with nosocomial pneumonia for *Legionella*.

**Antibiotic-Resistant Bacteria** Outbreaks of antibiotic resistance can depend on any of the following events: Darwinian selection of bacterial chromosomal mutations, spread of plasmid- and/or transposon-borne resistance among bacterial species, and (re)admission to the hospital of patients chronically infected with resistant bacteria. After the introduction of resistant strains, dissemination occurs by cross-infection on unwashed hands of caregivers or, occasionally, via personnel carriage and/or environmental contamination. Outbreak control depends on close laboratory surveillance, with early detection of problems; on the reinforcement of routine asepsis (e.g., hand washing); on the implementation of barrier precautions for all colonized and/or infected patients; on the use of patient-surveillance cultures to more fully ascertain the extent of patient colonization; and on the timely initiation of an epidemiologic investigation when rates increase. Colonized personnel who are implicated in nosocomial transmission and patients who pose a threat may be decontaminated; for example, colonization with methicillin-resistant *Staphylococcus aureus* may be controlled with oral antibiotics, including trimethoprim-sulfamethoxazole and rifampin, and with topical agents, including hexachlorophene or chlorhexidine and mupirocin. In a few ICUs, selective decontamination has been used successfully as a temporary emergency control measure for outbreaks of infection due to gram-negative bacilli.

The most recent bacterial-resistance problem to plague hospitals is the emergence of VRE. Initially an ICU problem, VRE have now spread onto general wards in many hospitals. VRE are particularly problematic because of a substantial "iceberg" effect (i.e., the fact that, for each individual with a clinical infection, many other patients are colonized); the occurrence of both gastrointestinal and skin colonization (reflecting fecal contamination on the skin of ill, hospitalized patients); and the propensity for these organisms to contaminate the patient's environment, which may increase the risk of cross-infection. Control of VRE requires strict attention to hand washing by personnel, concerted use of barrier precautions or cohort nursing for patients known to be colonized or infected, and emphasis on thorough cleaning of the rooms of these patients.

Spread of vancomycin resistance to *S. aureus* is a major concern. Clinical infections with methicillin-resistant *S. aureus* strains that exhibit reduced susceptibility to vancomycin have been reported in a few patients, usually in the setting of prolonged or repeated treatment with vancomycin. The detection of these strains requires augmented laboratory activities, and their identification should trigger an aggressive epidemiologic investigation and aggressive infection-control measures.

Because the excessive use of broad-spectrum antibiotics underlies many resistance problems, antibiotic-control policies (Table 134-2) must be considered a cornerstone of resistance-control efforts. Although the efficacy of antibiotic-control measures in reducing rates of antimicrobial resistance has not been proved in prospective controlled

trials, it seems worthwhile to restrict the use of particular agents to narrowly defined indications or possibly to cycle the use of antibiotic classes to limit selective pressure on the nosocomial flora.

## EMPLOYEE HEALTH SERVICE ISSUES

An institution's employee health service is a critical component of its infection-control efforts. New employees should be processed through the service, where a contagious-disease history can be taken; evidence of immunity to a variety of diseases, such as hepatitis B, chickenpox, measles, and rubella, can be sought; immunizations for hepatitis B, measles, rubella, and varicella can be given as needed and a reminder about the need for yearly influenza immunization can be imparted; baseline and "booster" purified protein derivative of tuberculin skin-testing can be performed; and education about personal responsibility for infection control can be initiated. Evaluations of employees should be codified to meet the requirements of accrediting and regulatory agencies.

The employee health service must have protocols for dealing with workers who have been exposed to contagious diseases, such as those percutaneously or mucosally exposed to the blood of patients infected with HIV. Postexposure HIV prophylaxis with a combination of antiretroviral agents (e.g., zidovudine and lamivudine, with or without indinavir or nelfinavir) is recommended. Protocols are also needed for dealing with caregivers who have common contagious diseases, such as chickenpox, group A streptococcal infections, respiratory infections, and infectious diarrhea, and for those who have less common but high-visibility public health problems, such as chronic hepatitis B or C or HIV infection, for which exposure-control guidelines have been published by theCDC and by the Society for Healthcare Epidemiology of America.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 135. HOSPITAL-ACQUIRED AND INTRAVASCULAR DEVICE-RELATED INFECTIONS - *Dori F. Zaleznik*

*Nosocomial infections* are defined as infections acquired during or as a result of hospitalization. Generally, a patient who has been in the hospital for<48 h and develops an infection is considered to have been incubating the infection before hospital admission. Most infections that become manifest after 48 h are considered to be nosocomial. A patient may develop a nosocomial infection after being discharged from the hospital if the organism apparently was acquired in the hospital. Surgical wound infection developing in the weeks after hospital discharge is an example of such nosocomial infection.

### INCIDENCE AND COSTS

Nosocomial infections contribute significantly to morbidity and mortality as well as to excess costs for hospitalized patients. It is estimated that 5% of patients admitted to an acute care hospital in the United States acquire a new infection, with>2 million nosocomial infections per year and an annual cost of >$2 billion. Some authorities estimate that the odds of death are doubled for patients who develop a nosocomial infection, although clearly such factors as underlying disease and severity of illness also play an important role in outcome.

Although immunosuppressed hosts are especially vulnerable to infections acquired in a hospital, common nosocomial infections occur even in immunocompetent hosts. The National Nosocomial Infections Surveillance (NNIS) Registry has been monitoring nosocomial infection rates since 1970. Its most recent report covers the period from October 1996 through April 1998 and includes both teaching and nonteaching hospitals and both small and large facilities. The most common nosocomial infections have remained the same. Urinary tract infections (UTIs), pneumonia, and surgical-site infections (SSIs, formerly termed wound infections) are most frequent. However, primary bloodstream infections, especially those associated with intravascular devices, have increased in frequency, as have infections in medical and surgical intensive care units (ICUs) and infections caused by antimicrobial-resistant pathogens.

The potential impact of nosocomial infections is considerable when assessed in terms of incidence, morbidity, mortality, and financial burden. Analyses of these factors examine nosocomial infections as both medical and economic issues. The clinical problem facing the physician is the development of a new fever in a patient in the hospital. In the evaluation of such a patient, information about the most common categories of infection may not be sufficient. Rather, the clinician must also use clinical clues from the patient's presentation and hospitalization to diagnose a nosocomial infection.

#### *Approach to the Patient*

The evaluation of a hospitalized patient with new fever should include a careful history (Chap. 17). Particular attention should be paid to symptoms of headache, cough, abdominal pain, diarrhea, flank pain, dysuria, urinary frequency, and leg pain. Other features related to the patient's hospitalization are also important, such as the presence and type of intravenous devices, the past or current use of a urinary catheter, the

surgical procedure conducted (if any), and the new medications administered, including those for surgical prophylaxis. The physical examination should be directed at possible sources of infection and should focus particularly on the skin (with a search for rash or embolic lesions); the lungs; the abdomen (especially the right upper quadrant); the costovertebral angles; surgical wounds; the calves; and current and old intravenous access sites (for signs of phlebitis). The laboratory evaluation of all hospitalized patients with new fever should include a complete blood count with differential, a chest radiograph, and blood and urine cultures. Other diagnostic tests to consider include liver function tests, plain-film or other studies of the abdomen, routine aerobic cultures of sputum or other relevant body fluids, and (in cases of diarrhea) testing of stool for *Clostridium difficile* toxin.

## CATEGORIES OF INFECTION

**Pneumonia** Certainly the astute clinician will question the patient thoroughly and perform a rapid comprehensive physical examination. One way to continue the approach to the hospitalized patient with a new fever is to consider potential infections that may be life-threatening, such as pneumonia. Most at risk for developing nosocomial pneumonia are patients in anICU, especially those who are intubated; patients with an altered level of consciousness, especially those with nasogastric tubes; elderly patients; patients with chronic lung disease; postoperative patients; and any of the above patients taking $H_2$blockers or antacids. Nosocomial pneumonia in theNNISRegistry is diagnosed 4 to 7 times per 1000 hospitalizations. Among patients on ventilators, the occurrence of pneumonia is estimated at 15 cases per 1000 ventilator days in medical and surgical ICUs. Mortality figures for nosocomial pneumonia are as high as 50%.

Oropharyngeal and gastric colonization plays a critical role in the pathogenesis of pneumonia in hospitalized patients. The oropharynx can become colonized by many species of aerobic gram-negative organisms within 48 h of the patient's hospitalization; aspiration occurs commonly during sleep and is increased by such factors as a nasogastric tube, altered consciousness, decreased gag reflex, or delayed gastric emptying. As for gastric colonization, bacterial counts in the stomach rise in the presence of medications that raise gastric pH, such as $H_2$blockers and antacids, as well as in malnourished, achlorhydric, and some elderly patients. The prevalence of pneumonia is reportedly two to three times higher among intubated patients receiving $H_2$blockers or antacids for stress-ulcer prophylaxis than among intubated patients receiving sucralfate, a medication that heals ulcers without altering gastric pH. Gastric colonization is believed to influence the development of pneumonia by retrograde colonization of the oropharynx. Ventilated patients are also at risk of developing pneumonia by exposure to bacteria leaking around the cuff of the endotracheal tube or to bacteria from nebulizers, condensate within ventilator circuits, or humidifiers.

Outside the ICU, pneumonia should be suspected when a patient develops a new cough, fever, leukocytosis, sputum production, and a new infiltrate on chest x-ray. Diagnosis can be complicated in patients with congestive heart failure who have concomitant chest x-ray abnormalities or in patients with chronic sputum production. Some organisms, such as *Legionella* spp., may not be associated with peripheral leukocytosis.

InICUpatients, especially those who are intubated, the signs of pneumonia are relatively subtle, and thus the diagnosis is often relatively complex. In particular, the chest x-rays are difficult to interpret, because fluid overload, congestive heart failure, and acute respiratory distress syndrome (ARDS) are all common findings in intubated patients. Polymorphonuclear leukocytes (PMNs) are often present on Gram-stained preparations of purulent secretions from these patients. An important clue to pneumonia is a change in the output or character of these secretions. If their volume or thickness increases or their color changes, a sputum Gram's stain should be performed and pneumonia seriously considered in the differential diagnosis. Serial Gram's stains are useful, as the number of PMNs may increase substantially and the type(s) of organisms may shift with the development of pneumonia. For example, the baseline sputum sample from an intubated patient may contain about 25 PMNs per high-power field and have mixed gram-positive and gram-negative organisms of several morphologic types in moderate numbers. On the day of a new fever, the same patient may have copious amounts of more tenacious sputum with more PMNs and a predominance of enteric-appearing gram-negative rods. Even without distinct changes in the chest x-ray, this patient would be considered to have developed pneumonia. Another subtle sign of pneumonia in the intubated patient is a requirement for change in ventilator settings in the absence of fluid overload, a mechanical alteration (e.g., a shift in endotracheal tube placement), or a pneumothorax.

The major organisms of concern in nosocomial pneumonia are gram-negative aerobic bacteria. *Pseudomonas aeruginosa* was the most common isolate in theNNISsurvey ofICUs, with a frequency of 21%; *Staphylococcus aureus* was next most common at 20%. *Acinetobacter* has become a more common pathogen in ventilator-associated pneumonia. While surveys of organisms are useful, it is essential to know which pathogens are common in a given institution, as hospitals and especially ICUs differ in their resident flora. In some institutions, methicillin-resistant *S. aureus*, *Stenotrophomonas* (formerly *Xanthomonas*) *maltophilia*, *Flavobacterium* spp., and even *Legionella* spp. may be of particular concern. Viruses such as respiratory syncytial virus and adenovirus are receiving increased attention as etiologic agents of nosocomial pneumonia in both adults and children. In the past, viruses have been underrepresented in statistics on the agents of nosocomial pneumonia because the diagnosis of viral infection is more difficult and because many microbiology laboratories do not have the capability to isolate viruses.

Antibiotic resistance is another important issue to address in the management of a hospitalized patient. An outgrowth of theNNISsurveys is Project ICARE, which tracks antibiotic usage patterns and resistance rates in a subset of NNIS institutions. Rates of resistance are generally higher in ICUsand track with increased use of antibiotics. *P. aeruginosa*, *Enterobacter* spp., and enterococci are the pathogens of greatest concern in the development of antibiotic resistance. In addition to knowing the sensitivity patterns of the hospital flora, one must consider whether a patient has received continuous or multiple courses of antibiotic therapy. To reduce the likelihood of altering the sensitivity patterns of the patient's flora, antibiotic courses for pneumonia should be kept as short as possible, with coverage as narrow as possible for the organism(s) involved.

**Bacteremia** Another potentially life-threatening nosocomial infection to consider in the evaluation of the patient with a new fever is bacteremia, which is usually related to the

presence of an intravascular device (Chap. 134). While many common nosocomial infections such as pneumonia orUTI can be accompanied by bacteremia, primary bacteremia is defined by isolation of a recognized pathogen from the blood without an infection at another site. One carefully controlled study reported bloodstream infection in 2.7% of admissions to a surgicalICU, with 50% mortality and a prolongation of hospitalization by 24 days in survivors.

One difficulty in assessing the significance of bacteremia is to distinguish true pathogens from contaminating skin flora. This distinction is especially important in establishing an infection of an indwelling intravascular catheter because organisms that inhabit the skin, such as coagulase-negative staphylococci, also frequently cause infection. The most common point of entry for infection related to intravascular devices is the insertion site, with spread of the infection along the outside of the device initially. Other means of entry for infecting organisms include introduction via contaminated infusates or tubing, ports, or leaking connections and hematogenous seeding of a catheter during bacteremia. While gram-negative aerobic bacilli are probably the most feared nosocomial bloodstream pathogens, the NNISdata for 1980 through 1989 showed that the isolation of these organisms had not increased in frequency over the decade. The frequency of bloodstream isolation increased the most for coagulase-negative staphylococci, with the next highest increase for *Candida* spp. Other leading causes of line-related bacteremia were *S. aureus* and enterococci. Subsequent studies confirmed these findings. Nosocomial endocarditis is an important, newly recognized entity that develops largely as a complication of invasive procedures or intravascular devices and may account for as many as 10% of cases of infective endocarditis.

Establishing an infection of an intravascular device or primary bacteremia as the cause of fever in a hospitalized patient is a diagnosis of exclusion. If a patient has a fever and signs of cutaneous involvement (erythema, induration, tenderness, or purulent drainage) at the insertion site of a catheter, full cultures should be performed, the vascular-access line removed, and the catheter tip sent for quantitative culture. Studies have correlated the growth of³15 colonies from a catheter tip with infection of the line. More commonly, the exit site does not show signs of infection, and there is considerable debate about the necessity of removing a line from a febrile patient at that point. Although line changes over a guidewire have been shown to be safe, unless another site of infection is obvious, it is generally advisable to remove the line and to change the site when a patient develops a new fever. The traditional teaching is that an infected intravenous device should be removed. In current practice, however, especially with surgically implanted intravenous catheters, a decision may be made to attempt treatment with antibiotics while leaving the catheter in place. This practice is often successful when the infecting organism is a coagulase-negative *Staphylococcus* species but is less often effective with other organisms, particularly *Candida* spp. and gram-negative bacilli. Salvage of catheters used for hemodialysis is especially important and has been successfully accomplished with infections caused by a variety of organisms.

Another controversial management issue is whether to draw blood for culture through a line. While some studies report a correlation in the 90% range between culture results for blood drawn through vascular-access lines and those for peripheral blood, the former cultures can be either false-positive or false-negative. If the line culture is positive and

no peripheral blood has been drawn, it is impossible to determine whether the patient has true bacteremia or the culture merely reflects bacteria associated with the line. Whether bacteremia is high- or low-grade and whether it is sustained or transient may influence the duration of antibiotic therapy and cannot be determined from cultures of blood specimens obtained through a line.

An area of considerable interest and controversy is the prevention of catheter-related infections through the use of intravenous devices impregnated with chlorhexidine/silver sulfadiazine or minocycline/rifampin. A meta-analysis of 11 studies found a decrease in both catheter colonization and catheter-related bacteremia with chlorhexidine/silver sulfadiazine-impregnated catheters, with associated cost savings. One multicenter prospective randomized trial directly compared the two types of catheters and found the minocycline/rifampin-impregnated catheter to be superior. Antibiotic-resistant strains were not recovered in this trial, although concern has been raised that antibiotic impregnation may increase the development of resistance. The several other studies that do not support these findings include one in which the incidence of bacteremia did not decrease with the use of chlorhexidine/silver sulfadiazine-impregnated catheters.

**Surgical-Site Infection** Evaluation of fever in the postoperative patient must include careful evaluation of the surgical wound. AlthoughSSIreportedly accounts for 19% of nosocomial infections, the true incidence of postoperative wound infection is difficult to assess, particularly at a time when many patients are hospitalized for relatively short periods. In a number of studies, careful follow-up for the development of SSI after discharge -- especially observation of the wound by a trained observer, such as a nurse -- has shown the actual rates of SSI in all categories of surgery to be greater than the reported rates. SSI rates vary from 4.6 to 8.2% for nonteaching and large teaching hospitals, respectively. Rates also vary by procedure, with abdominal surgery resulting in the highest rates.

Risk factors for the development of postoperative wound infection include the presence of a drain; a long preoperative length of stay, with the rates doubling for each week of preoperative hospitalization; preoperative shaving of the field, especially if performed [3]24 h beforehand; a long duration of surgery; and the presence of an untreated remote infection. Infection rates also vary with the surgeon. Perioperative antibiotic prophylaxis has been shown to decrease rates of wound infection in a number of careful studies, including those of clean surgical procedures. Antibiotic coverage after the surgical wound is closed has not been shown to provide additional benefit.

A surgical wound should be examined for localized tenderness and induration, fluctuance, drainage of purulent material, and dehiscence of sutures. Mechanical factors, as well as infection, can cause wound dehiscence. Sternal wounds following cardiac surgery are of special concern because the consequences of infection can be severe. The surface of the wound may not present an obvious cause for concern, but ongoing fevers, serous drainage, and especially the development of rocking or instability of the sternum may be sufficient cause for surgical exploration of the wound in some cases. Mediastinitis or sternal osteomyelitis is a severe complication of cardiac surgery. Wounds associated with the placement of prosthetic devices, such as mechanical joints, are also of special concern. Infection of these wounds can lead to infection of the prosthesis, and clearance of prosthetic joint infections generally requires surgical

removal of the device.

The most common pathogens causingSSI are coagulase-negative *Staphylococcus* and *S. aureus*, but antibiotic-resistant bacteria and fungi are also becoming more frequent etiologies. Early infections may be associated with organisms that produce rapid, progressive skin infection, such as group A *Streptococcus* and *Clostridium* spp. Group A *Streptococcus* has been identified in some cases of recurrent infection of saphenous-vein graft harvest sites.

**Urinary Tract Infection** UTI, the most common type of nosocomial infection, is generally the easiest to treat and has the least severe sequelae. Four principal risk factors have been associated repeatedly with the development of UTI in hospitalized patients: female sex, prolonged urinary catheterization, lack of systemic antibiotic therapy, and breach of appropriate catheter care. The administration of systemic antibiotics to patients with urinary catheters in place for 1 to 5 days has been associated with a decrease in rates of bacteriuria. For patients with catheters in place for ³6 days, however, this benefit is not observed.

The pathogenesis of catheter-associatedUTIappears to differ in men and women. In women, the typical mechanism involves periurethral colonization with fecal flora and tracking of organisms up the catheter to the bladder; thus the pathogenesis resembles that of UTI in noncatheterized female patients, in whom bacteria track up the short female urethra. In contrast, periurethral colonization often cannot be demonstrated in men; most infections seem to arise from intraluminal spread of organisms to the bladder. Some organisms, such as *Proteus* and *Pseudomonas* spp., appear to facilitate the growth along the inside of the urinary catheter of a biofilm that encrusts and obstructs the flow of urine.

UTIis certainly an extremely common nosocomial infection; however, it is important to define this type of infection precisely. Especially in the evaluation of a febrile hospitalized patient, it is crucial to think carefully about all possible sources of infection and not to assume that UTI is the probable cause. In patients who have had urinary catheters in place for a number of days, fever, dysuria, frequency, leukocytosis, and especially flank pain or costovertebral angle tenderness are highly suggestive of bladder infection or pyelonephritis. In patients with fever but no other symptoms or signs referable to the urinary tract, one should look for ancillary findings suggestive of urinary tract involvement, such as white blood cells without epithelial cells in the urine sediment or leukocyte esterase or nitrite on urinalysis. A urine culture positive for a single organism should not be accepted as definitive evidence of UTI in an asymptomatic patient. While one might treat the febrile patient who has a positive urine culture with antibiotics, it is prudent to repeat the culture before the institution of therapy. Inability to recover any organism or the same organism on repeat culture, particularly if the patient does not respond to antibiotics, should raise questions about the validity of the diagnosis of UTI. In addition, isolation of two or more bacteria from a single specimen is most likely due to contamination unless there is reason to suspect a bladder diverticulum or a perinephric abscess.

**Other Infectious Sources of Fever** Several other types of infection may cause fever in the hospitalized patient and should be considered in the differential diagnosis of new

fever. In patients who have received antibiotics (even a single dose as surgical prophylaxis), antibiotic-associated diarrhea may develop. This condition is usually caused by the spore-forming organism *C. difficile*, which produces toxins that cause diarrhea. Some patients may appear quite toxic with this infection, with high fevers, leukocytosis, and profuse diarrhea. The organism is quite hardy and is difficult to eradicate from the hospital environment. The hands of hospital personnel have been implicated as a mode of transmission of this organism, as have electronic rectal thermometers. The colon may become colonized with *C. difficile* while the patient is in the hospital, but -- particularly if the patient is still taking antibiotics when sent home -- diarrhea may not develop until after discharge.

Unless patients are consuming foods from outside the hospital, food-borne diarrheal illness is uncommon among hospitalized patients. Thus, an extensive stool evaluation is generally not cost-effective in the management of these patients.

Other infections to consider in the hospitalized patient include decubitus ulcers, particularly in patients in chronic-care wards or confined to bed rest for prolonged periods, and sinusitis, especially in intubated patients.

## NONINFECTIOUS SOURCES OF FEVER

A consideration of several common noninfectious causes of fever in hospitalized patients is part of a thorough evaluation of new fever. Drug treatment is the foremost noninfectious cause of fever. Drug fever may occur with or without an accompanying rash or eosinophilia and can be caused by a new medication or by medications the patient has been receiving for some time. Particular agents associated with drug fever include phenytoin, $H_2$blockers, procainamide, and antibiotics, most notably sulfonamides. Even drug-associated fevers can be quite high in some patients and may take up to 5 days to resolve after discontinuation of treatment with the offending agent. Other noninfectious causes of fever include phlebitis, often at the site of an old intravenous line and sometimes followed by suppurative thrombophlebitis with clots or septic emboli, and pulmonary emboli, especially in patients undergoing prolonged bed rest; prophylactic heparin or mechanical boots are often used to reduce the risk of pulmonary embolism in the latter patients. Other entities to consider include tissue necrosis following surgery, trauma, or burns; hematomas; pancreatitis; atelectasis; and acalculous cholecystitis.

## CONCLUSION

The range of possibilities for the etiology of a new fever in a hospitalized patient is quite broad. An attention to detail, a careful history and physical examination, and a knowledge of the infections and organisms likely to cause nosocomial problems usually lead to an accurate diagnosis.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 136. INFECTIONS IN TRANSPLANT RECIPIENTS - *Robert Finberg*, *Joyce Fingeroth*

The evaluation of infections in transplant recipients involves consideration of both the donor and the recipient of the transplanted organ. Infections following transplantation are complicated by the use of drugs that are necessary to enhance the likelihood of survival of the transplanted organ but that also cause the host to be immunocompromised. Thus what might have been a latent or asymptomatic infection in an immunocompetent donor or in the recipient prior to therapy becomes a life-threatening problem when the recipient becomes immunosuppressed.

A variety of organisms have been transmitted by organ transplantation (Table 136-1). Careful attention to the sterility of the medium used to process the organ combined with meticulous microbiologic evaluation reduces rates of transmission of bacteria that may be present or grow in the organ culture medium. From 2% to >20% of donor kidneys are estimated to be contaminated with bacteria -- in most cases, with the organisms that colonize the skin or grow in the tissue culture medium used to bathe the donor kidney while it awaits implantation. The reported rate of bacterial contamination of transplanted bone marrow is as high as 17% but is most commonly ~1%. The use of enrichment columns and monoclonal-antibody depletion procedures results in a higher incidence of contamination. Approximately 2% of cryopreserved marrow and peripheral blood stem cells transfused as part of treatment for cancer are contaminated. In one series of patients receiving contaminated products, 14% had fever or bacteremia, but none died. Results of cultures performed at the time of cryopreservation and at the time of thawing were helpful in guiding therapy for the recipient.

In many transplantation centers, transmission of infections that may be latent or clinically inapparent in the donor organ has resulted in the development of specific donor-screening protocols. In addition to ordering serologic studies focusing on viruses such as herpes-group viruses [herpes simplex virus (HSV) 1, HSV-2], varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus (HHV) 6, Epstein-Barr virus (EBV), HHV-8, hepatitis B and C viruses, and HIV and on parasites such as *Toxoplasma gondii*, clinicians caring for organ donors should consider assessing stool (for parasites) and skin testing for *Mycobacterium tuberculosis*. It is expected that the recipient will have been likewise assessed. This chapter considers aspects of infection unique to various transplantation settings.

### INFECTIONS IN BONE MARROW AND HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Bone marrow or hematopoietic stem cell transplantation for either immunodeficiency or cancer results in a transient state of complete immune incompetence. Immediately after transplantation, both phagocytes and immune cells (T and B cells) are absent, and the host is extremely susceptible to infection. The reconstitution that follows transplantation has been likened to maturation of the immune system in neonates. The analogy does not entirely predict infections seen in bone marrow transplant (BMT) and hematopoietic stem cell transplant (HSCT) recipients, however, because the new marrow matures in an old host who has several latent infections already.

## TIMING OF INFECTIONS

In the first month after bone marrow or hematopoietic stem cell transplantation, infectious complications are similar to those in granulocytopenic patients receiving chemotherapy for acute leukemia (Chap. 85). Because of the anticipated 1- to 4-week duration of neutropenia in this population, many centers give prophylactic antibiotics to patients upon initiation of chemotherapy. Prophylactic trimethoprim-sulfamethoxazole or ciprofloxacin decreases the incidence of gram-negative bacteremia among these patients.

In the second month after transplantation, a major concern (particularly in allogeneicBMT/HSCTrecipients) isCMVdisease (Chap. 185), which rarely has its onset earlier than 14 days after transplantation and may become evident up to 4 months after the procedure (most commonly at 1 to 3 months). In cases in which the donor marrow is depleted of T cells [to prevent graft-versus-host disease (GVHD) or eliminate a T cell tumor], the disease may be manifested earlier. Patients who receive ganciclovir (for prophylaxis, preemptive treatment, or treatment; see below) may develop CMV infection even later than 4 months after transplantation; treatment appears to delay the development of the normal immune response to CMV infection. Although CMV disease may present as isolated fever, cytopenia, or gastrointestinal disease, the foremost cause of death from CMV infection in this setting is pneumonia.

The diagnosis of pneumonia inBMT/HSCTrecipients poses some special problems (Table 85-5). Because patients have undergone treatment with multiple chemotherapeutic agents and sometimes radiation, their differential diagnosis should include -- in addition to bacterial pneumonia -- CMVpneumonitis, pneumonia of other viral or fungal etiology, parasitic pneumonia, diffuse alveolar hemorrhage, and chemical- or radiation-associated pneumonitis. Since fungal disease and viruses such as respiratory syncytial virus (RSV), parainfluenza virus (types 1, 2, and 3), influenza A and B viruses, and adenovirus are also causes of pneumonia in this setting, it is important to diagnose CMV specifically (see below). *M. tuberculosis* has been an uncommon cause of pneumonia among BMT/HSCT recipients in western countries (<0.1 to 0.2%) but is common in Hong Kong (5.5%) and in countries where the prevalence of tuberculosis is high. The exposure history of the recipient is clearly critical in an assessment of posttransplantation infections.

Episodes of bacteremia due to encapsulated organisms and reactivation ofVZV mark the late posttransplantation period (6 months after bone marrow reconstitution). Because of the high and prolonged risk of *Pneumocystis carinii* pneumonia (especially among patients being treated for hematologic malignancies), most patients should be maintained on prophylactic doses of trimethoprim-sulfamethoxazole starting 1 month after engraftment and continuing for at least 1 year. Such prophylaxis may also protect patients seropositive for *T. gondii*, which may cause pneumonia as well as central nervous system (CNS) lesions. The advantages of maintaining patients on daily trimethoprim-sulfamethoxazole for 1 year after transplantation include protection against *Listeria monocytogenes* and nocardial disease as well as late bacterial infections with pneumococci and *Haemophilus influenzae*, which are a consequence of the inability of the immature bone marrow to respond to polysaccharide antigens. In patients withGVHD who require prolonged or indefinite courses of steroids and other

immunosuppressive agents (e.g., cyclosporine, tacrolimus), there is a high risk of fungal infections (usually with *Candida* or *Aspergillus*), even after engraftment and resolution of neutropenia.

## VIRAL INFECTIONS

BMT/HSCTrecipients are susceptible to infection with a variety of viruses, including reactivation syndromes caused by mostHHVs(Table 136-2) and infections caused by viruses that circulate in the community.

**Herpes Simplex Virus** Within the first 2 weeks after transplantation, most patients who are seropositive forHSV-1 excrete the virus in the oropharynx. The ability to isolate HSV declines with time. Administration of prophylactic acyclovir to seropositiveBMT/HSCTrecipients has been shown to reduce mucositis and prevent HSV pneumonia (a rare condition reported almost exclusively in BMT recipients). Both esophagitis (usually due to HSV-1) and anogenital disease (commonly induced by HSV-2) may be prevented with acyclovir prophylaxis.*For further discussion, see Chap. 182.*

**Varicella-Zoster Virus** Reactivation of herpes zoster may occur within the first month but more commonly occurs several months after transplantation (seePlate IID-37). Reactivation rates are ~40% for allogeneic recipients and 25% for autologous recipients. Localized zoster can spread in an immunosuppressed patient. Fortunately, disseminated disease can usually be controlled with high doses of acyclovir. Because of the high incidence of dissemination of herpes zoster among patients with skin lesions, acyclovir is given prophylactically in some centers to prevent severe disease. Low doses of acyclovir (400 mg orally, three times daily) appear to be effective in preventing reactivation ofVZV. However, acyclovir also inhibits the development of VZV-specific immunity. Thus, its administration for only 6 months after transplantation does not prevent zoster from occurring when treatment is stopped. Some data suggest that administration of low doses of acyclovir for an entire year after transplantation is effective and may eliminate most cases of posttransplantation zoster.*For further discussion, see Chap. 183.*

**Cytomegalovirus** The onset of CMVdisease usually comes between 30 and 90 days after transplantation, when the granulocyte count is adequate but immunologic reconstitution has not occurred. CMV may cause interstitial pneumonia, bone marrow suppression, or graft failure. With the standard use of CMV-negative or filtered blood products, primary CMV infection should be a risk in allogeneic transplantation only when the donor is CMV-seropositive and the recipient is CMV-seronegative. Reactivation disease or superinfection with another strain from the donor is also common in CMV-positive recipients, and most seropositive patients who undergo bone marrow transplantation excrete CMV, with or without clinical findings. Serious CMV disease is much more common among allogeneic recipients and is often associated withGVHD. In addition to pneumonia and marrow suppression (and, less often, graft failure), manifestations of CMV disease inBMT/HSCTrecipients include fever with or without arthralgias, myalgias, and esophagitis. CMV ulcerations occur in both the lower and upper gastrointestinal tract, and it may be difficult to distinguish diarrhea due to GVHD from that due to CMV infection. The finding of CMV in the liver of a patient with GVHD

does not necessarily mean that CMV is responsible for hepatic enzyme abnormalities.

Management ofCMVdisease inBMT/HSCTrecipients includes strategies directed at prophylaxis, suppression, preemptive therapy, or treatment. Prophylaxis results in a lower incidence of disease at the cost of treating many patients who otherwise would not require therapy. Because of the high fatality rate associated with CMV pneumonia in these patients and the difficulty of early diagnosis of CMV infection, prophylactic ganciclovir has been used in some centers and has been shown to abort CMV disease during the period of maximal vulnerability (from engraftment to day 120 after transplantation). The foremost problem with the administration of this drug relates to adverse effects, which include dose-related bone marrow suppression (thrombocytopenia, leukopenia, anemia, and pancytopenia). Because the frequency of CMV pneumonia is lower among autologous BMT recipients (2 to 7%) than among allogeneic BMT recipients (10 to 40%), prophylaxis in the former group will not become the rule until a less toxic antiviral agent becomes available.

Like prophylaxis, suppressive treatment, which targets patients with polymerase chain reaction evidence ofCMV or CMV-positive urine cultures, entails the unnecessary treatment of many individuals (on the basis of a laboratory test that is not highly predictive of disease) with drugs that have adverse effects. Currently, because of the neutropenia associated with ganciclovir inBMT/HSCTrecipients, a preemptive approach -- treatment of those patients in whose blood CMV is detected by an antigen or DNA test -- is used at most centers. This approach is almost as effective as prophylaxis or suppression and causes less toxicity. The use of the leukocyte antigen test for CMV disease (fluorescent staining of leukocytes for CMV antigens) allows earlier diagnosis but leads to treatment of more patients than would be treated on the basis of blood cultures, with a consequent increase in very late disease (>120 days after transplantation). The use of quantitative viral load assays, which are not dependent on circulating polymorphonuclear leukocytes, should permit early accurate diagnosis in the future.

Treatment ofCMVpneumonia inBMT/HSCTrecipients requires both intravenous immune globulin (IVIG) and ganciclovir. In patients who cannot tolerate ganciclovir, foscarnet is a useful alternative, although it may produce nephrotoxicity and electrolyte imbalance. Transfusion of CMV-specific T cells from the donor decreased viral load in a small series of patients; this result suggests that immunotherapy may play a role in the treatment of this disease in the future.*For further discussion, see Chap. 185.*

**Human Herpesviruses 6 and 7**HHV-6, the cause of exanthem subitum in children (Chap. 185), is a ubiquitous herpesvirus that reactivates (as determined by culture of the virus from the blood) in ~50% of transplant recipients between 2 and 4 weeks after surgery. In some cases, reactivation of HHV-6 appears to be associated with neutropenia; since, likeCMV, this virus can be found in marrow cells, it is possible that HHV-6 reactivation is responsible for some of the neutropenia that follows bone marrow transplantation. Although encephalitis developing after transplantation has been associated with HHV-6 in cerebrospinal fluid (CSF), the causality of the association is not well defined. HHV-6 DNA is sometimes found in lung samples after transplantation. However, its role in pneumonitis is unclear. While HHV-6 has been shown to be sensitive to foscarnet (and in some instances to ganciclovir) in vitro, the efficacy of

antiviral treatment has not been well studied. Little is known about the related herpesvirus HHV-7 or its role in posttransplantation infection.*For further discussion, see Chap. 185.*

**Epstein-Barr Virus** PrimaryEBVinfection can be fatal to transplant recipients; EBV reactivation can cause EBV-B cell lymphoproliferative disease (LPD), which may also be fatal to patients taking immunosuppressive drugs. The localization of EBV to B cells leads to several interesting phenomena inBMT/HSCTrecipients. The marrow ablation that occurs as part of the BMT/HSCT procedure may eliminate latent EBV from the host. Infection can then be reacquired immediately after transplantation by transfer of infected donor B cells. Alternatively, transplantation from a seronegative donor may result in cure. The recipient is then at risk for a second primary infection.

EBV-LPDcan develop in the recipient's B cells (if any should survive marrow ablation) but is more likely to be a consequence of outgrowth of infected donor cells. Both lytic and latent EBV replication are more likely during immunosuppression (e.g., they are associated withGVHD and the use of antibodies to T cells). Although less likely in autologous transplantation, reactivation can occur in T cell-depleted autologous recipients (e.g., patients being treated for a T cell lymphoma with marrow depletion using antibodies to T cells). EBV-LPD, which usually becomes apparent 1 to 3 months after engraftment, can cause high fevers and cervical adenopathy resembling the symptoms of infectious mononucleosis but more commonly presents as an extranodal mass. The incidence of 0.6% among allogeneicBMT/HSCTrecipients contrasts with figures of ~5% for renal transplant recipients and up to 20% for cardiac transplant patients. In all cases, EBV-LPD is more likely to occur with continued immunosuppression (especially that caused by the use of antibodies to T cells and cyclosporine or tacrolimus).

EBV-specific T cells generated from the donor have been used experimentally to prevent and to treat EBV-LPDin the allogeneic recipient. Some studies indicate that EBV-LPD can be treated with antibodies to B cell surface antigens. Use of an anti-CD20 monoclonal antibody (Rituximab) to treat B cell lymphomas that express this surface protein has elicited some dramatic responses. Studies are in progress to assess efficacy in EBV-LPD, in which the involved B cells commonly bear CD20. The role of antivirals is uncertain because no available agents have been documented to have activity against latent EBV infection. Ganciclovir has been postulated to have activity on the basis of its ability to inhibit proliferation of B cells, but this activity is associated with toxicity. Both interferona and retinoic acid have been used in the treatment of EBV-LPD, as hasIVIG, but no large studies have assessed the efficacy of these agents. Chemotherapeutic regimens have been used as a last resort, even though patients' tolerance and long-term results have been disappointing in this setting.*For further discussion, see Chap. 184.*

**Human Herpesvirus 8** TheEBV-related gamma herpesvirusHHV-8, which is causally associated with Kaposi's sarcoma, with primary effusion lymphoma, and sometimes with multicentric Castleman's disease, has rarely resulted in disease inBMT/HSCTrecipients. The reasons may be a relatively low seroprevalence in the population and the limited duration of profound T cell suppression after bone marrow/hematopoietic stem cell transplantation.*For further discussion, see Chap. 185.*

**Other (Nonherpes) Viruses** Both RSVand parainfluenza viruses, particularly type 3, can cause severe or even fatal pneumonia inBMTrecipients. Infections with both of these agents sometimes occur as disastrous nosocomial epidemics. Therapy with aerosolized ribavirin as well as RSV immunoglobulin or monoclonal antibody to RSV (Palivizumab) has been reported to lessen the severity of RSV disease, but there are no large studies to prove efficacy. Influenza is also seen in BMT recipients and generally mirrors the presence of infection in the community. Several drugs are available for the treatment of influenza (amantadine/rimantadine, ribavirin?) but have limited effects, primarily reducing symptoms and shortening the duration of illness. The newly approved neuraminidase inhibitors are active against both influenza A virus and influenza B virus. Their role in ameliorating disease in this patient population is unknown. Adenovirus can be isolated from BMT recipients at rates varying from 5 to 18%. Although hemorrhagic cystitis, pneumonia, and fatal disseminated infection have been reported, adenovirus infection, which (likeCMVinfection) usually occurs in the first or second month after transplantation, is often asymptomatic. Therapy with intravenous ribavirin is questionably effective. Cidofovir has proved effective in animal models and in case reports. Infections with parvovirus B19 (presenting as anemia or occasionally pancytopenia) and enteroviruses (sometimes fatal) can occur. Pleconaril, a newly developed capsid-binding agent, is being studied for treatment of enterovirus infection. Rotaviruses are a common cause of gastroenteritis in BMT/HSCTrecipients. BK and, to a lesser extent, JC virus (polyomavirus hominis 1 and 2, respectively) are found in the urine of some transplant recipients. BK viruria may be associated with hemorrhagic cystitis. Progressive multifocal leukoencephalopathy caused by JC virus is rare among BMT/HSCT recipients compared with the rate among patients with impaired T cell function due to HIV infection. There is no known treatment for this disease; however, cidofovir and other agents are under study.

## INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Morbidity and mortality among solid organ transplant recipients have been reduced by the use of more effective antibiotics. The organisms that cause infections in recipients of solid organ transplants are different from those that infectBMT/HSCTrecipients because solid organ recipients do not go through a period of neutropenia. As the transplantation procedure involves surgery, however, solid organ recipients are subject to infections at anastomotic sites and to wound infections. Compared with BMT/HSCT recipients, organ transplant patients are immunosuppressed for more prolonged periods (often permanently). Thus they are susceptible to the same organisms as patients with chronically impaired T cell immunity (Chap. 85, especiallyTable 85-1).

During the early period (<1 month after transplantation), infections are most often caused by extracellular bacteria (staphylococci, streptococci, *Escherichia coli*, other gram-negative organisms), which often originate in surgical wound or anastomotic sites. The spectrum of infection is largely determined by the type of transplant.

In subsequent weeks, the consequences of the administration of agents that suppress cell-mediated immunity and of the acquisition or reactivation (from the transplanted organ) of viruses and parasites become apparent.CMVinfection is often a problem in the first 6 months after transplantation and may present as severe systemic disease or as

an infection of the transplanted organ.HHV-6 reactivation (assessed by blood culture) occurs within the first 2 to 4 weeks after transplantation and may be associated with fever and granulocytopenia.

CMVis associated not only with generalized immunosuppression but also with organ-specific, rejection-related syndromes: glomerulopathy in kidney transplant recipients, bronchiolitis obliterans in lung transplant recipients, vasculopathy in heart transplant recipients, and the vanishing bile duct syndrome in liver transplant recipients. A complex interplay between increased CMV replication and enhanced graft rejection is well established: Increasing immunosuppression leads to increased CMV replication, which is associated with graft rejection. For this reason, considerable attention has been focused on the diagnosis, treatment, and prophylaxis of CMV infection in organ transplant recipients.

Beyond 6 months after transplantation, infections characteristic of patients with defects in cell-mediated immunity -- e.g., infections with *Listeria*, *Nocardia*, various fungi, and other intracellular pathogens -- may be a problem. Elimination of these late infections will not be possible until specific tolerance to the transplanted organ can be achieved without the administration of drugs that lead to generalized immunosuppression. Meanwhile, vigilance, prophylaxis/preemptive therapy (when indicated), and rapid diagnosis and treatment of infections can be lifesaving in solid organ transplant recipients, who, unlike mostBMTrecipients, continue to be immunosuppressed.

Solid organ transplant recipients are susceptible toEBV-LPDfrom as early as 2 months to many years after transplantation. The prevalence of this complication is increased by potent and prolonged use of T cell-suppressive drugs. The condition may be reversed (in some cases) by decreasing the degree of immunosuppression. Among organ transplant patients, those with heart and lung transplants -- who receive the most intensive immunosuppressive regimens -- are most likely to develop EBV-LPD, particularly in the lungs. Although disease usually originates in recipient B cells, several cases of donor origin have been reported. There is a notable tendency for EBV-LPD to develop in the transplanted organ. High organ-specific content of B lymphoid tissues (i.e., bronchial-associated lymphoid tissue in the lung), anatomic factors (i.e., lack of access of host T cells to the transplanted organ because of disturbed lymphatics), and differences in major histocompatibility loci between the host T cells and the organ (i.e., lack of cell migration or lack of effective T cell/macrophage cooperation) may result in defective elimination of EBV-infected B cells.

## INFECTIOUS COMPLICATIONS OF KIDNEY TRANSPLANTATION (See Table 136-3)

**Early Infections** Infections developing soon after kidney transplantation are often caused by bacteria associated with skin or wound infections. Some data indicate a role for perioperative antibiotic prophylaxis, and many centers give cephalosporins or a penicillin with an aminoglycoside to decrease the risk of postoperative complications. Urinary tract infections developing soon after transplantation are usually related to anatomic alterations resulting from surgery. Such early infections may require prolonged treatment (e.g., 6 weeks of antibiotic administration for pyelonephritis). Urinary tract infections that occur >6 months after transplantation do not seem to be associated with the high rate of pyelonephritis or relapse seen with infections that occur in the first 3

months and may be treated for shorter periods.

Prophylaxis with trimethoprim-sulfamethoxazole [1 double-strength tablet (800 mg sulfamethoxazole, 160 mg trimethoprim) per day] for the first 4 months after transplantation decreases the incidence of early and middle-period infections (see below and Table 136-4).

**Middle-Period Infections** Because of continuing immunosuppression, kidney transplant recipients are predisposed to lung infections characteristic of those in patients with T cell deficiency (i.e., infections with intracellular bacteria, mycobacteria, nocardiae, fungi, viruses, and parasites). The high mortality associated with *Legionella pneumophila* infection (Chap. 151) led to the closing of renal transplant units in hospitals with endemic legionellosis.

About 50% of all renal transplant recipients presenting with fever 1 to 4 months after transplantation have evidence ofCMVdisease; CMV itself accounts for the fever in over two-thirds of cases and thus is the predominant pathogen during this period. CMV infection (Chap. 185) may also present as arthralgias or myalgias. During this period, this infection may represent primary disease (in the case of a seronegative recipient of a kidney from a seropositive donor) or may present as reactivation disease or superinfection. Patients may have atypical lymphocytosis. Unlike immunocompetent patients, however, they often do not have lymphadenopathy or splenomegaly. Therefore, clinical suspicion and laboratory confirmation are necessary for diagnosis. The clinical syndrome may be accompanied by bone marrow suppression (particularly leukopenia). CMV also causes glomerulopathy and is associated with an increased incidence of other opportunistic infections. Because of the frequency and severity of CMV disease, a considerable effort has been made to prevent and treat it in renal transplant recipients. Administration of an immune globulin preparation enriched with antibodies to CMV (CMV-Ig) decreases the incidence in the group at highest risk for severe infections (seronegative recipients of seropositive kidneys). Ganciclovir is useful for the treatment of serious CMV disease. One study showed a significant (50%) reduction in CMV disease and rejection at 6 months in patients who received prophylactic valacyclovir (an acyclovir congener) for the first 90 days after renal transplantation. If confirmed, these results will likely change practice.

Infection with the other herpes-group viruses may become evident within 6 months after transplantation or later. Early after transplantation,HSV may cause either oral or anogenital lesions that are usually responsive to acyclovir. Large ulcerating lesions in the anogenital area may lead to bladder and rectal dysfunction as well as predisposing to bacterial infection.VZV may cause fatal disseminated infection in nonimmune kidney transplant recipients, but in immune patients reactivation zoster usually does not disseminate outside the dermatome; thus disseminated VZV infection is a less fearsome complication in kidney transplantation than in bone marrow transplantation.HHV-6 may reactivate and (although usually asymptomatic) may be associated with fever, rash, marrow suppression, or encephalitis.

EBVreactivation disease is more serious; it may present as an extranodal proliferation of B cells that invade theCNS, nasopharynx, liver, small bowel, heart, and transplanted kidney. The disease is diagnosed by the finding of a proliferation of EBV-positive B

cells. The incidence of EBV-LPDis higher among patients given high doses of cyclosporine, tacrolimus, or other immunosuppressive agents (including anti-T cell antibodies). Fortunately, disease often regresses once immunocompetence is restored.HHV-8 infection can be transmitted with the donor kidney and is associated with the development of Kaposi's sarcoma in the recipient. Kaposi's sarcoma (primary vs. reactivation of HHV-8) often appears within 1 year after transplantation, although the range of onset times is wide (1 month to ~20 years).

The papovaviruses BK and JC (polyomaviruses hominis 1 and 2) have been cultured from the urine of kidney transplant recipients (as they have from that ofBMTrecipients). The excretion of BK virus is associated with ureteral strictures and that of JC virus with progressive multifocal leukoencephalopathy (rare). Adenoviruses may persist with continued immunosuppression in these patients.

Kidney transplant recipients are also subject to infections with other intracellular organisms. These patients may develop pulmonary infections with *Nocardia*, *Aspergillus*, and *Mucor* as well as infections with other pathogens in which the T cell/macrophage axis plays an important role. In patients without intravenous catheters, *L. monocytogenes* is the most common cause of bacteremia³1 month after renal transplantation. Kidney transplant recipients may develop *Salmonella* bacteremia, which can lead to endovascular infections and require prolonged therapy. Pulmonary infections with *P. carinii* are common unless the patient is maintained on trimethoprim-sulfamethoxazole prophylaxis. *Nocardia* infection (Chap. 165) may present in the skin, bones, lungs, orCNS(where it usually takes the form of single or multiple brain abscesses). *Nocardia* infection generally occurs ³1 month after transplantation and may follow immunosuppressive treatment for an episode of rejection. Pulmonary findings are nonspecific: localized disease with or without cavities is most common, but the disease may disseminate. The diagnosis is made by culture of the organism from sputum or from the involved nodule. As with *P. carinii*, prophylaxis with trimethoprim-sulfamethoxazole appears to be efficacious in the prevention of disease. The occurrence of *Nocardia* infections>2 years after transplantation suggests that a long-term prophylactic regimen may be justified.

Toxoplasmosis can occur in seropositive patients, usually developing in the first few months after kidney transplantation. Again, trimethoprim-sulfamethoxazole is helpful in prevention. In endemic areas, histoplasmosis, coccidioidomycosis, and blastomycosis may cause pulmonary infiltrates or disseminated disease.

**Late Infections** Late infections (>6 months after kidney transplantation) includeCMVretinitis and a variety ofCNScomplications. Patients (particularly those whose immunosuppression has been increased) are at risk for subacute meningitis due to *Cryptococcus neoformans*. Cryptococcal disease may present in an insidious manner (sometimes as a skin infection before the development of clear CNS findings). *Listeria* meningitis may have an acute presentation and requires prompt therapy to avoid a fatal outcome.

Patients who continue to take glucocorticoids are predisposed to infection. "Transplant elbow" is a recurrent bacterial infection in and around the elbow that is thought to result from a combination of poor tensile strength of the skin of steroid-treated patients and

steroid-induced proximal myopathy that requires patients to push themselves up with their elbows to get out of chairs. Bouts of cellulitis (usually caused by *Staphylococcus aureus*) recur until patients are provided with elbow protection.

Kidney transplant recipients are susceptible to invasive fungal infections -- such as those due to *Aspergillus* and *Rhizopus*, which may present as superficial lesions before dissemination. Mycobacterial infection (particularly that with *M. marinum*) can be diagnosed by skin examination. Infection with *Prototheca wickerhamii* (an achlorophyllic alga) has been diagnosed by skin biopsy. Warts caused by human papillomaviruses (HPVs) are a late consequence of persistent immunosuppression; local therapy is usually satisfactory.

## HEART TRANSPLANTATION

**Early Infections** Sternal wound infection and mediastinitis are early complications of heart transplantation. An indolent course is common, with fever or a mildly elevated white blood cell count preceding the development of site tenderness or drainage. Clinical suspicion based on evidence of sternal instability and failure to heal may lead to the diagnosis. Although common residents of the skin (e.g., *S. aureus* and *S. epidermidis*) as well as gram-negative organisms (e.g., *Pseudomonas aeruginosa*) and fungi (e.g., *Candida*) are often involved, mediastinitis in these patients (in rare cases) can also be due to *Mycoplasma hominis* (Chap. 178). Since this organism requires an anaerobic environment for growth and may be difficult to see on conventional medium, the laboratory should be alerted that *M. hominis* infection is suspected. *M. hominis* mediastinitis has been cured with a combination of surgical debridement (sometimes requiring muscle-flap placement) plus clindamycin and tetracycline. Organisms associated with mediastinitis may be cultured from accompanying pericardial fluid.

**Middle-Period Infections** *T. gondii* (Chap. 217) resident in the heart of a seropositive donor may be transmitted to a seronegative recipient. Thus serologic screening for *T. gondii* infection is important before and in the months after cardiac transplantation. Rarely, active disease can be introduced at the time of transplantation. The overall incidence of toxoplasmosis is so high in this setting that some prophylaxis is warranted. Although alternatives are available, the most frequently used agent is trimethoprim-sulfamethoxazole, which prevents infection with *Pneumocystis*, *Nocardia*, and other bacterial pathogens.CMV has also been transmitted by heart transplantation.CNSinfections can be caused by *Toxoplasma*, *Nocardia*, and *Aspergillus*. *L. monocytogenes* meningitis should be considered in heart transplant recipients with fever and headache.

CMVinfection is associated with poor outcomes after heart transplantation. The virus is usually cultivable 1 to 2 months after transplantation, causes manifestations (usually fever and atypical lymphocytosis, often associated with leukopenia and thrombocytopenia) at 2 to 3 months, and produces severe disease (e.g., pneumonia) at 3 to 4 months. Seropositive recipients usually develop cultivable virus faster than patients whose primary CMV infection is a consequence of transplantation. Between 40 and 70% of patients develop symptomatic CMV disease in the form of (1) CMV pneumonia, the most likely form of CMV disease to be fatal; (2) CMV esophagitis and gastritis, sometimes accompanied by abdominal pain with or without ulcerations and

bleeding; and (3) the CMV syndrome consisting of CMV in the blood with fever, leukopenia, thrombocytopenia, and hepatic enzyme abnormalities. Ganciclovir is efficacious in the treatment of CMV infection; prophylaxis with ganciclovir or possibly with other antivirals, as described for renal transplantation, may reduce the incidence of CMV-related disease.

**Late Infections** EBVinfection usually presents as a lymphoma-like proliferation of B cells late after heart transplantation, particularly in patients maintained on heavy immunosuppression. A subset of heart and heart-lung transplant recipients may develop early (within 2 months) fulminant EBV-LPD. Treatment includes the reduction of immunosuppression if possible and the consideration of B cell antibodies (Rituximab), immunomodulatory agents, or chemotherapy, as discussed earlier under bone marrow/hematopoietic stem cell transplantation.HHV-8-associated disease, including primary effusion lymphoma, has been reported in heart transplant recipients. Prophylaxis for *P. carinii* infection is required for these patients (see below).

**LUNG TRANSPLANTATION**

**Early Infections** It is not surprising that lung transplants are predisposed to the development of pneumonia. The combination of ischemia and the resulting mucosal damage together with accompanying denervation and lack of lymph drainage probably contributes to the high rate of pneumonia (66% in one series). The prophylactic use of high doses of broad-spectrum antibiotics for the first 3 or 4 days after surgery decreases the incidence of pneumonia. Gram-negative pathogens (Enterobacteriaceae and *Pseudomonas* species) are troublesome in the first 2 weeks after surgery (the period of maximal vulnerability). Pneumonia can also be caused by *Candida* (possibly as a result of colonization of the donor lung), *Aspergillus*, and *Cryptococcus*.

Mediastinitis may occur at an even higher rate among lung transplant recipients than among heart transplant recipients and most commonly develops within 2 weeks of surgery. Pneumonitis due to CMV(which may be transmitted as a consequence of transplantation) usually presents between 2 weeks and 3 months after surgery, with primary disease occurring later than reactivation disease.

**Middle-Period Infections** The incidence ofCMVinfection, either reactivated or primary, is between 75 and 100% if either the donor or the recipient is seropositive for CMV. CMV-induced disease appears to be most severe in recipients of lung and heart-lung transplants. Whether this severity relates to the mismatch in lung antigen-presenting and host immune cells or is attributable to other (nonimmune) factors is not known. More than half of lung transplant recipients with symptomatic CMV disease have pneumonia. Difficulty in distinguishing the radiographic picture of CMV infection from organ rejection further complicates therapy. CMV can also cause bronchiolitis obliterans in lung transplants. The development of pneumonitis related toHSV has led to the prophylactic use of acyclovir. Such prophylaxis may also decrease rates of CMV disease, but ganciclovir is more active against CMV and is also active against HSV. Ganciclovir prophylaxis for CMV disease in lung transplant recipients is recommended.

**Late Infections** The incidence of *P. carinii* infection (which may present with a paucity of findings) is high among lung and heart-lung transplant recipients. Some form of

prophylaxis for *P. carinii* pneumonia is indicated in all organ transplant situations (Tables 136-4 and136-5). Trimethoprim-sulfamethoxazole prophylaxis for 12 months after transplantation may be sufficient to prevent *P. carinii* disease in patients whose degree of immunosuppression is not increased.

As in other transplant recipients, infection withEBV may cause either a mononucleosis-like syndrome orLPD. The tendency of the B cell blasts to present in the lung appears to be greater after lung transplantation than after the transplantation of other organs. Reduction of immunosuppression causes remission in some cases, but airway compression can be fatal and more rapid intervention may therefore become necessary. The approach to EBV-LPD is similar to that described in other sections.

## LIVER TRANSPLANTATION

**Early Infections** As in other types of transplantation, early bacterial infections are a major problem after liver transplantation. Many centers administer systemic broad-spectrum antibiotics for the first 5 days after surgery, even in the absence of documented infection. However, despite prophylaxis, infectious complications are common and are correlated with the duration of the surgical procedure and the type of biliary drainage. An operation lasting>12 h is associated with an increased likelihood of infection. Patients who have a choledochojejunostomy with drainage of the biliary duct to a Roux-en-Y jejunal bowel loop have more fungal infections than those whose bile is drained via a choledochocholedochostomy with anastomosis of the donor common bile duct to the recipient common bile duct.

Peritonitis and intraabdominal abscesses are common complications of liver transplantation. Bacterial peritonitis may result from biliary leaks and primary or secondary infection after leakage of bile. Peritonitis in liver transplant recipients is often polymicrobial, commonly involving enterococci, aerobic gram-negative bacteria, staphylococci, anaerobes, or *Candida*. Only one-third of patients with intraabdominal abscesses have bacteremia. Abscesses within the first month after surgery may occur not only over the liver but also in the spleen, pericolic area, and pelvis. Treatment includes antibiotic administration and drainage as necessary.

Liver transplant patients have a high incidence of fungal infections, and the occurrence of fungal infection (often candidiasis) correlates with preoperative use of glucocorticoids, a long duration of treatment with antibacterial agents, and posttransplantation use of immunosuppressive agents.

**Middle-Period Infections** The development of postsurgical biliary stricture predisposes patients to cholangitis. These patients may lack the characteristic signs and symptoms of cholangitis: fever, abdominal pain, and jaundice. Alternatively, these findings may be present but may suggest graft rejection. The diagnosis of cholangitis in liver transplant recipients therefore requires documentation of bacteremia or demonstration of aggregated neutrophils in bile duct biopsy specimens. Unfortunately, invasive studies of the biliary tract (either T-tube cholangiography or endoscopic retrograde cholangiopancreatography) may themselves lead to cholangitis. For this reason, many clinicians recommend prophylaxis with antibiotics covering gram-negative organisms and anaerobes when these procedures are performed in liver transplant recipients.

Viral hepatitis is a common complication of liver transplantation (Chap. 295). Reactivation of hepatitis B and C infections, for which transplantation may be performed, is problematic. To prevent hepatitis B infection, high-dose intravenous hepatitis B immune globulin is often administered. The long-term efficacy of lamivudine (3TC) in inhibiting hepatitis B viral replication after transplantation is being studied. A combination of interferon a and ribavirin is being tested for treatment/prophylaxis of hepatitis C infection.

As in other transplantation settings, reactivation disease with herpes-group viruses is common (Table 136-2). Herpesviruses can be transmitted in donor organs. AlthoughCMVhepatitis occurs in ~4% of liver transplant recipients, it is usually not so severe as to require retransplantation. CMV disease develops in the majority of seronegative recipients of organs from CMV-positive donors, but fatality rates are lower in liver transplant recipients than in lung or heart-lung transplant recipients. Disease due to CMV is associated with the vanishing bile duct syndrome after liver transplantation. Patients respond to treatment with ganciclovir; prophylaxis with CMV immune globulin and acyclovir or oral ganciclovir may modify disease. A role forHHV-6 in posttransplantation fever and leukopenia has been proposed.EBV-LPDafter liver transplantation shows a propensity for involvement of the liver, and such disease may be of donor origin.

## PANCREAS TRANSPLANTATION

Transplantation of the pancreas is complicated by early abdominal infection in ~20 to 40% of cases. To prevent contamination of the allograft with enteric bacteria and yeasts, some surgeons, instead of draining the pancreas through the bowel, drain secretions into the urinary tract or bladder. A cuff of duodenum is often used in the anastomosis between the pancreatic graft and the bladder. In addition to bicarbonate loss, this technique causes a high rate of urinary tract infection (30 to 40%) and sterile cystitis. Over the long term, bowel drainage is better tolerated. An alternative method -- the transplantation of islet cells only -- may eliminate the problems characteristically posed by wound and urinary tract sepsis in pancreas transplant recipients.

Issues related to the development ofCMVinfection,EBV-LPD, and infections with opportunistic pathogens in patients receiving a pancreas are similar to those in other solid organ transplant recipients.

## MISCELLANEOUS INFECTIONS IN SOLID ORGAN TRANSPLANTATION

**Indwelling Intravenous Catheter Infections** The prolonged use of indwelling intravenous catheters for administration of medication, blood products, and nutrition is common in diverse transplantation settings and poses a risk of local and bloodstream infection. Significant insertion-site infection is most commonly caused by *S. aureus*. Bloodstream infection most frequently develops within a week of catheter placement or in patients who become neutropenic. Coagulase-negative staphylococci are the most common isolates from the blood.**For further discussion of differential diagnosis and therapeutic options, see Chap. 85.*

**Tuberculosis** The incidence of tuberculosis occurring within 12 months after solid organ transplantation ranges broadly worldwide (0.35 to 15%), reflecting prevalences in local populations. Nonrenal transplantation,GVHDwithin 6 months, and intensity of immunosuppression are predictive of tuberculosis reactivation and development of disseminated disease in a host with latent disease. Tuberculosis has rarely been transmitted from the donor organ. In contrast to the low mortality inBMT/HSCTrecipients, mortality in solid organ transplant patients is reported to be 29%. Isoniazid toxicity has not been a significant problem except in the liver transplantation setting.

**Virus-Associated Malignancies** In addition to malignancy associated with gammaherpesvirus infection (EBV,HHV-8) and simple warts (HPV), transplant recipients, particularly those who require long-term immunosuppression, are more likely than the general population to develop tumors that are virus-associated or suspected of being virus-associated. The interval to tumor development is usually >1 year. Transplant recipients develop nonmelanoma skin or lip cancers that, in contrast to de novo skin cancers, have a high squamous cell-to-basal cell ratio. Whether HPV plays a major role in these lesions is being investigated. Cervical and vulvar carcinomas, quite clearly associated with HPV, develop with increased frequency in female transplant recipients. In renal transplant recipients, rates of melanoma are modestly increased and rates of cancers of the kidney and bladder are increased.

## VACCINATION OF TRANSPLANT RECIPIENTS

In addition to receiving antibiotic prophylaxis, transplant recipients should be vaccinated against likely pathogens (Table 136-6). In the case ofBMTrecipients, optimal responses cannot be achieved until after reconstitution, despite previous immunization of both donor and recipient. Recipients of allogeneic BMTs must be reimmunized if they are to be protected against pathogens. The situation is less clear-cut in the case of autologous transplantation. T and B cells in the peripheral blood may reconstitute the response if they are transferred in adequate numbers. However, cancer patients (particularly those with Hodgkin's disease, in whom vaccination has been extensively studied) who are undergoing chemotherapy do not respond normally to immunization, and titers of antibodies to infectious agents fall more rapidly than in healthy individuals. Therefore, even immunosuppressed patients who have not had marrow transplants may need booster vaccine injections. If memory cells are specifically eliminated as part of a marrow "cleanup" procedure, it will be necessary to reimmunize the recipient with a new primary series. Optimal times for immunizations of different transplant populations are being evaluated. Immunization of household and other contacts (including health care personnel) against influenza every season is likely to benefit the patient by preventing local spread.

In the absence of compelling data as to optimal timing, it is reasonable to administer the pneumococcal and *H. influenzae* type b conjugate vaccines to both autologous and allogeneicBMTrecipients 12 months after transplantation and again 12 months later (since the response to the initial vaccine dose is weak in the early posttransplantation period). These two vaccines are particularly important for patients who have undergone splenectomy. In addition, *Neisseria meningitidis* polysaccharide vaccine, diphtheria vaccine, tetanus vaccine, and inactivated polio vaccine can all be given at these same

intervals (12 and 24 months after transplantation). Some authorities recommend a new primary series for tetanus/diphtheria and inactivated polio vaccine (vaccination 12, 14, and 16 months after transplantation). Because of the risk of spread, household contacts of BMT recipients (or of patients immunosuppressed as a result of chemotherapy) should receive only inactivated polio vaccine. Live-virus measles/mumps/rubella (MMR) vaccine can be given to autologous BMT recipients 24 months after transplantation and to most allogeneic BMT recipients at the same point if they are not receiving maintenance therapy with immunosuppressive drugs and do not have ongoingGVHD. The risk of spread from a household contact is lower for MMR than for polio vaccine. In patients who have active GVHD and/or are taking high maintenance doses of glucocorticoids, it may be prudent to avoid all live-virus vaccines. In the absence of detectable antibody titers, vaccination to prevent hepatitis B and hepatitis A also seems advisable.

In the case of solid organ transplant recipients, administration of all the usual vaccines and of the indicated booster doses should be completed before immunosuppression, if possible, to maximize responses. For patients taking immunosuppressive agents, the administration of pneumococcal vaccine should be repeated every 5 years. No data are available for meningococcal polysaccharide vaccine, but it is probably reasonable to administer it along with the pneumococcal vaccine or more frequently (every 3 years for persons with significant exposure risk). *H. influenzae* conjugate vaccine is safe and should be efficacious in this population; therefore, its administration before transplantation is recommended. Booster doses of this vaccine are not recommended for adults. Solid organ transplant recipients who continue to receive immunosuppressive drugs (glucocorticoids, cyclosporine) should not receive live-virus vaccines. A person in this group exposed to measles should be given immune globulin. Similarly, an immunocompromised patient who is seronegative for varicella and who comes into contact with a person who has chickenpox should be given varicella-zoster immune globulin as soon as possible (and certainly within 96 h) or, if this is not possible, started immediately on a 10- to 14-day course of acyclovir therapy. Susceptible household contacts of transplant recipients should receive live attenuatedVZVvaccine, but vaccinees should avoid direct contact with the patient if a rash develops.

Immunocompromised patients who travel may benefit from some but not all vaccines. In general, they should receive any killed or inactivated vaccine preparation appropriate to the area they are visiting; this recommendation includes the vaccines for Japanese encephalitis, hepatitis A and B, poliomyelitis, meningococcal infection, and typhoid. The live typhoid vaccines are not recommended for use in most immunocompromised patients, but inactivated typhoid or the purified polysaccharide vaccine can be used. Live yellow fever vaccine should not be administered. Phenol-inactivated cholera vaccine is probably of little use in this setting. On the other hand, immunization with the purified-protein hepatitis B vaccine is indicated if patients are likely to be exposed. Patients who will reside for>6 months in areas where hepatitis B is common (Africa, Southeast Asia, the Middle East, Eastern Europe, parts of South America, and the Caribbean) should receive hepatitis B vaccine. Inactivated hepatitis A vaccine should be used in the appropriate setting (Chap. 122). If hepatitis A vaccine is not administered, travelers should consider receiving passive protection with immune globulin (the dose depending on the duration of travel in the high-risk area).

(Bibliography omitted in Palm version)

Back to Table of Contents

## SECTION 4 -APPROACH TO THERAPY FOR BACTERIAL DISEASES

# 137. TREATMENT AND PROPHYLAXIS OF BACTERIAL INFECTIONS - *Gordon L. Archer*, *Ronald E. Polk*

The development of drugs that prevent and cure bacterial infections is one of the twentieth century's major contributions to human longevity and quality of life. Antibacterial agents are among the most commonly prescribed drugs of any kind worldwide. Used appropriately, these drugs are lifesaving. However, their indiscriminate use drives up the cost of health care, leads to a plethora of side effects and drug interactions, and fosters the emergence of bacterial resistance, rendering previously valuable drugs useless. The rational use of antibacterial agents depends on an understanding of their mechanisms of action, pharmacokinetics, toxicities, and interactions; bacterial strategies for resistance; and bacterial susceptibility in vitro. In addition, patient-associated parameters, such as the site of infection and the immune and excretory status of the host, are critically important to appropriate therapeutic decisions. This chapter provides specific data required for making an informed choice of antibacterial agent.

## MECHANISMS OF ACTION

Antibacterial agents, like all antimicrobial drugs, are directed against unique targets not present in mammalian cells. The goal is to limit toxicity to the host and maximize chemotherapeutic activity affecting invading microbes only. The mechanisms of action of the antibacterial agents to be discussed in this section are summarized in Table 137-1 and are depicted inFig. 137-1.

### INHIBITION OF CELL-WALL SYNTHESIS

One major difference between bacterial and mammalian cells is the presence in bacteria of a rigid wall external to the cell membrane. The wall protects bacterial cells from osmotic rupture, which would result from the cell's usual marked hyperosmolarity (by up to 20 atm) relative to the host environment. The structure conferring cell-wall rigidity and resistance to osmotic lysis in both gram-positive and -negative bacteria is peptidoglycan, a large, covalently linked sacculus that surrounds the bacterium. In gram-positive bacteria, peptidoglycan is the only layered structure external to the cell membrane and is thick (20 to 80 nm); in gram-negative bacteria, there is an outer membrane external to a very thin (1-nm) peptidoglycan layer.

Chemotherapeutic agents directed at any stage of the synthesis, export, assembly, or cross-linking of peptidoglycan lead to inhibition of bacterial cell growth and, in most cases, to cell death. Peptidoglycan is composed of (1) a backbone of two alternating sugars, *N*-acetylglucosamine and *N*-acetylmuramic acid; (2) a chain of four amino acids that extends down from the backbone (stem peptides); and (3) a peptide bridge that cross-links the peptide chains. Peptidoglycan is formed by the addition of subunits (a sugar with its five attached amino acids) that are assembled in the cytoplasm and transported through the cytoplasmic membrane to the cell surface. Subsequent cross-linking is driven by cleavage of the terminal stem-peptide amino acid. Antibacterial agents act to inhibit cell-wall synthesis in several ways, as described below.

*Bacitracin*, a cyclic peptide antibiotic, inhibits the conversion to its active form of the lipid carrier that moves the water-soluble cytoplasmic peptidoglycan subunits through the cell membrane to the cell exterior. Cell-wall subunits accumulate in the cytoplasm and cannot be added to the growing peptidoglycan chain.

*Glycopeptides* (vancomycin and teicoplanin) are high-molecular-weight antibiotics that bind to the terminal D-alanine-D-alanine component of the stem peptide while the subunits are external to the cell membrane but still linked to the lipid carrier. This binding sterically inhibits the addition of subunits to the peptidoglycan backbone.

*b-Lactam antibiotics* (penicillins, cephalosporins, carbapenems, and monobactams;Table 137-2), characterized by a four-memberedb-lactam ring, prevent the cross-linking reaction called *transpeptidation*. The energy for attaching a peptide cross-bridge from the stem peptide of one peptidoglycan subunit to another is derived from the cleavage of a terminal D-alanine residue from the subunit stem peptide. The cross-bridge amino acid is then attached to the penultimate D-alanine by transpeptidase enzymes. The b-lactam ring of the antibiotic forms an irreversible covalent acyl bond with the transpeptidase enzyme (probably because of the antibiotic's steric similarity to the enzyme's D-alanine-D-alanine target), preventing the cross-linking reaction. Transpeptidases and similar enzymes involved in cross-linking are called *penicillin-binding proteins* (PBPs) because they all have active sites that bind b-lactam antibiotics.

Virtually all the antibiotics that inhibit bacterial cell-wall synthesis are bactericidal. That is, they eventually result in the cell's death due to osmotic lysis. However, much of the loss of cell-wall integrity following treatment with cell wall-active agents is due to the bacteria's own cell-wall remodeling enzymes (autolysins) that cleave peptidoglycan bonds in the normal course of cell growth. In the presence of antibacterial agents that inhibit cell-wall growth, autolysis proceeds without normal cell-wall repair; weakness and eventual cellular lysis occur.

## INHIBITION OF PROTEIN SYNTHESIS

Most of the antibacterial agents that inhibit protein synthesis interact with the bacterial ribosome. The difference between the composition of bacterial and mammalian ribosomes gives these compounds their selectivity.

*Aminoglycosides* (gentamicin, kanamycin, tobramycin, streptomycin, netilmicin, neomycin, and amikacin) are a group of structurally related compounds containing three linked hexose sugars. They exert a bactericidal effect by binding irreversibly to the 30S subunit of the bacterial ribosome and blocking initiation of protein synthesis. The reason for the lethal effect of aminoglycosides (as opposed to the largely bacteriostatic effect of other protein synthesis-inhibiting antibacterial drugs, including the macrolides, the lincosamides, chloramphenicol, and tetracycline) is not completely understood. Uptake of aminoglycosides and their penetration through the cell membrane constitute an aerobic, energy-dependent process. Thus, aminoglycoside activity is markedly reduced in an anaerobic environment. *Spectinomycin*, an aminocyclitol antibiotic, also acts on the 30S ribosomal subunit but has a different mechanism of action from the

aminoglycosides and is bacteriostatic rather than bactericidal.

*Macrolides* (erythromycin, clarithromycin, and azithromycin) consist of a large lactone ring to which sugars are attached. They bind specifically to the 50S portion of the bacterial ribosome. After attachment of mRNA to the initiation site of the 30S ribosomal subunit (the process blocked by aminoglycosides), the 50S subunit becomes bound to the 30S component to form the 70S ribosomal complex, and protein chain elongation proceeds. Binding of macrolides to the 50S ribosomal subunit inhibits protein chain elongation.

*Lincosamides* (clindamycin and lincomycin), although structurally unrelated to macrolides, bind to a site on the 50S ribosome nearly identical to the binding site for macrolides. Although the mechanism and site of action of macrolides and lincosamides are similar, the number and types of bacteria against which these two groups of agents are active differ.

*Chloramphenicol* consists of a single aromatic ring and a short side chain. This antibiotic binds reversibly to the 50S portion of the bacterial ribosome at a site close to but not identical with the binding sites of the macrolides and lincosamides. The ribosomal binding of chloramphenicol inhibits peptide bond formation.

*Tetracyclines* (tetracycline, doxycycline, and minocycline) consist of four aromatic rings with various substituent groups. They interact reversibly with the bacterial 30S ribosomal subunit, blocking the binding of aminoacyl tRNA to the mRNA-ribosome complex. This mechanism is markedly different from that of the aminoglycosides, which also bind to the 30S subunit. The specificity of tetracyclines for bacteria depends both on their selectivity for bacterial ribosomes and on their requirement for active, energy-dependent transport into the bacterial cell by a system not found in mammalian cell membranes.

*Mupirocin* (pseudomonic acid) is produced by the bacterium *Pseudomonas fluorescens*. Its mechanism of action is unique in that it inhibits the enzyme isoleucine tRNA synthetase by competing with bacterial isoleucine for its binding site on the enzyme. Inhibition of this enzyme depletes cellular stores of isoleucine-charged tRNA and therefore leads to a cessation of protein synthesis. The antibiotic is selective for bacteria because mammalian isoleucine tRNA synthetase lacks affinity for the compound.

## INHIBITION OF BACTERIAL METABOLISM

The *antimetabolites* are all synthetic compounds that interfere with bacterial synthesis of folic acid. Products of the folic acid synthesis pathway function as coenzymes for the one-carbon transfer reactions that are essential for the synthesis of thymidine, all purines, and several amino acids. Inhibition of folate synthesis leads to cessation of bacterial cell growth and, in some cases, to bacterial cell death. The principal antibacterial antimetabolites are sulfonamides (sulfisoxazole, sulfadiazine, and sulfamethoxazole) and trimethoprim.

*Sulfonamides* are structural analogues of *p*-aminobenzoic acid (PABA), one of the three structural components of folic acid (the other two being pteridine and glutamate). The

first step in the synthesis of folic acid is the addition of PABA to pteridine by the enzyme dihydropteroic acid synthetase. Sulfonamides compete with PABA as substrates for the enzyme. The selective effect of sulfonamides is due to the fact that bacteria synthesize folic acid, while mammalian cells cannot synthesize the cofactor and must have exogenous supplies. However, the activity of sulfonamides can be greatly reduced by the presence of excess PABA or by the exogenous addition of end products of one-carbon transfer reactions (e.g., thymidine and purines). High concentrations of the latter substances may be present in some infections as a result of tissue and white cell breakdown, compromising sulfonamide activity.

*Trimethoprim* is a diaminopyrimidine, a structural analogue of the pteridine moiety of folic acid. It is a competitive inhibitor of dihydrofolate reductase; this enzyme is responsible for reduction of dihydrofolic acid to tetrahydrofolic acid, the essential final component in the folic acid synthesis pathway that is necessary for all one-carbon transfer reactions. Like the sulfonamides, trimethoprim is bactericidal in the absence of thymine but is only bacteriostatic when this pyrimidine is present in high concentration. The selective antibacterial activity of trimethoprim is based on the extreme sensitivity of bacterial dihydrofolate reductase to inhibition by this drug in comparison with the mammalian enzyme. The bacterial enzyme is approximately 50,000 times more sensitive to such inhibition.

## INHIBITION OF NUCLEIC ACID SYNTHESIS OR ACTIVITY

Numerous antibacterial compounds have disparate effects on nucleic acids. The *quinolones*, including nalidixic acid and its fluorinated derivatives (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin), are synthetic compounds that inhibit the activity of the A subunit of the bacterial enzyme DNA gyrase as well as topoisomerase IV. DNA gyrase and topoisomerases are responsible for negative supercoiling of DNA, an essential conformation for DNA replication in the intact cell. Inhibition of the activity of DNA gyrase and topoisomerase IV is lethal to bacterial cells. The antibiotic *novobiocin* also interferes with the activity of DNA gyrase, but it interferes with the B subunit.

*Rifampin*, used primarily against *Mycobacterium tuberculosis*, is also active against a variety of other bacteria. Rifampin binds tightly to the B subunit of bacterial DNA-dependent RNA polymerase, thus inhibiting transcription of DNA into RNA. Mammalian-cell RNA polymerase is not sensitive to the compound.

*Nitrofurantoin*, a synthetic compound, causes DNA damage. The nitrofurans, compounds containing a single five-membered ring, are reduced by a bacterial enzyme to highly reactive, short-lived intermediates that are thought to cause DNA strand breakage, either directly or indirectly.

*Metronidazole*, a synthetic imidazole, is active against a wide range of anaerobic bacteria and protozoa. This activity is totally dependent on the organism's anaerobic electron-transport system for energy production. In the presence of this system, the nitro group of metronidazole is reduced to a series of transiently produced, reactive intermediates that are thought to cause DNA damage. The unique redox system of anaerobes accounts for the selective antibacterial activity of metronidazole. This

compound is also a mutagen and a radiosensitizer of hypoxic mammalian cells.

### ALTERATION OF CELL-MEMBRANE PERMEABILITY

The *polymyxins* (polymyxin B and colistin, or polymyxin E) are cyclic, basic polypeptides. They behave as cationic, surface-active compounds that disrupt the permeability of both the outer and the cytoplasmic membranes of gram-negative bacteria.

*Gramicidin A* is a polypeptide of 15 amino acids that acts as an ionophore, forming pores or channels in lipid bilayers.

## MECHANISMS OF RESISTANCE

Some bacteria have *intrinsic resistance* to certain classes of antibacterial agents (e.g., obligate anaerobic bacteria to aminoglycosides and gram-negative bacteria to vancomycin). Clearly these agents can never be used alone in the treatment of infections caused by resistant bacteria. In addition, bacteria that are ordinarily susceptible to antibacterial agents can acquire resistance. *Acquired resistance* is one of the major limitations to effective antibacterial chemotherapy. Resistance can develop by mutation of resident genes or by acquisition of new genes. New genes mediating resistance are usually spread from cell to cell by way of mobile genetic elements such as plasmids, transposons, and bacteriophages. The resistant bacterial populations flourish in areas of high antimicrobial use, where they enjoy a selective advantage over susceptible populations.

The major mechanisms used by bacteria to resist the action of antimicrobial agents are inactivation of the compound, alteration or overproduction of the antibacterial target through mutation of the target protein's gene, acquisition of a new gene that encodes a drug-insensitive target, decreased permeability of the cell envelope to the agent, and active elimination of the compound from the periplasm or interior of the cell. Specific mechanisms of bacterial resistance to the major antibacterial agents are outlined below, summarized inTable 137-1, and depicted inFig. 137-1.

### b-LACTAMS

Bacteria develop resistance to b-lactam antibiotics by a variety of mechanisms. Most common is the destruction of the drug byb-lactamases. Theb-lactamases of gram-negative bacteria are confined to the periplasm, between the inner and outer membranes, while gram-positive bacteria secrete their b-lactamases into the surrounding medium. These enzymes have a higher affinity for the antibiotic than the antibiotic has for its target. Binding results in hydrolysis of theb-lactam ring. Genes encodingb-lactamases have been found in both chromosomal and extrachromosomal locations and in both gram-positive and -negative bacteria; these genes are often on mobile genetic elements. One strategy that has been devised for circumventing resistance mediated byb-lactamases is to combine the susceptibleb-lactam with an inhibitor that avidly binds the inactivating enzyme, preventing its attack on the antibiotic. Unfortunately, the inhibitors (e.g., clavulanic acid, sulbactam, and tazobactam) do not bind all classes of b-lactamase and thus cannot be depended on to prevent the

inactivation of b-lactam antibiotics by such enzymes. No b-lactam antibiotic or inhibitor has been produced that can resist all of the manyb-lactamases that have been identified.

A second mechanism of bacterial resistance to b-lactam antibiotics is an alteration inPBPtargets so that the PBPs have a markedly reduced affinity for the drug. While this alteration may occur by mutation of existing genes, the acquisition of new PBP genes (as in staphylococcal resistance to methicillin) or of new pieces of PBP genes (as in streptococcal, gonococcal, and meningococcal resistance to penicillin) is more important.

A final resistance mechanism is the coupling, in gram-negative bacteria, of a decrease in outer-membrane permeability with rapid efflux of the antibiotic from the periplasm to the cell exterior. Mutations of genes encoding outer-membrane proteins called *porins* decrease the entry ofb-lactam antibiotics into the cell, while additional proteins form channels that actively pump b-lactams out of the cell. Resistance of Enterobacteriaceae to some cephalosporins and resistance of *Pseudomonas* spp. to cephalosporins and ureidopenicillins are the best examples of this mechanism.

## VANCOMYCIN

Clinically important resistance to vancomycin was first described among enterococci in France in 1988. Vancomycin-resistant enterococci have subsequently become disseminated worldwide. The genes encoding resistance are carried on plasmids that can transfer themselves from cell to cell. Resistance is mediated by enzymes that substitute D-lactate for D-alanine on the peptidoglycan stem peptide so that there is no longer an appropriate target for vancomycin binding. This alteration does not appear to affect cell-wall integrity, however. This type of acquired vancomycin resistance is so far confined to enterococci and is seen in *Enterococcus faecium* rather than in the more common pathogen *E. faecalis*. Most clinically important staphylococci (i.e., *Staphylococcus aureus* and *S. epidermidis*) remain susceptible. However, in 1996, an isolate of *S. aureus* recovered from an infected patient in Japan was shown to be eight times less susceptible to vancomycin than were usual isolates. Since that report, an additional three *S. aureus* isolates with intermediate susceptibility to vancomycin have been recovered from infected patients in the United States, as have numerous coagulase-negative staphylococci with reduced vancomycin susceptibility. These isolates have not acquired the genes that mediate vancomycin resistance in enterococci but are mutant bacteria with markedly thickened cell walls. These mutants were apparently selected in patients who were undergoing prolonged vancomycin therapy.

## AMINOGLYCOSIDES

The most common aminoglycoside resistance mechanism is inactivation of the antibiotic. Aminoglycoside-modifying enzymes, usually encoded on plasmids, transfer phosphate, adenyl, or acetyl residues from intracellular molecules to hydroxyl or amino side groups on the antibiotic. The modified antibiotic is less active because of diminished binding to its ribosomal target. Modifying enzymes that can inactivate any of the available aminoglycosides have been found in both gram-positive and -negative bacteria.

A second aminoglycoside resistance mechanism that has been identified predominantly in clinical isolates of *Pseudomonas aeruginosa* is decreased antibiotic uptake, presumably due to alterations in the bacterial outer membrane.

## MACROLIDES AND LINCOSAMIDES

Resistance in gram-positive bacteria, the usual target organisms for macrolides and lincosamides, is due to the production of an enzyme -- most commonly plasmid-encoded -- that methylates ribosomal RNA, interfering with binding of the antibiotics to their target. Methylation mediates resistance to erythromycin, clarithromycin, azithromycin, and clindamycin. Streptococci can also actively efflux these compounds.

## CHLORAMPHENICOL

Most bacteria resistant to chloramphenicol produce a plasmid-encoded enzyme, chloramphenicol acetyltransferase, that inactivates the compound by acetylation.

## TETRACYCLINES

The most common mechanism of tetracycline resistance in gram-negative bacteria is a plasmid-encoded active-efflux pump that is inserted into the cytoplasmic membrane and extrudes antibiotic from the cell. Resistance in gram-positive bacteria is due either to active efflux or to ribosomal alterations that diminish binding of the antibiotic to its target. Genes involved in ribosomal protection are found on mobile genetic elements.

## MUPIROCIN

Although the topical compound mupirocin was relatively recently introduced into clinical use, resistance is already becoming widespread in some areas. The mechanism appears to be either mutation of the target isoleucine tRNA synthetase so that it is no longer inhibited by the antibiotic or plasmid-encoded production of a form of the target enzyme that binds mupirocin poorly.

## TRIMETHOPRIM AND SULFONAMIDES

The most prevalent mechanism of resistance to trimethoprim and the sulfonamides in both gram-positive and -negative bacteria is the acquisition of plasmid-encoded genes that produce a new, drug-insensitive target -- specifically, an insensitive dihydrofolate reductase for trimethoprim and an altered dihydropteroate synthetase for sulfonamides.

## QUINOLONES

Resistance to the newer fluoroquinolones emerged rapidly among *Staphylococcus* and *Pseudomonas* spp. after the introduction of these agents. The most common mechanism is the development of one or more mutations in target DNA gyrases and topoisomerase IV that prevent the antibacterial agent from interfering with the activity of the enzyme. Some gram-negative bacteria develop mutations that both decrease

outer-membrane porin permeability and cause active drug efflux from the cytoplasm. Mutations that result in active quinolone efflux are also found in gram-positive bacteria.

### RIFAMPIN

Bacteria rapidly become resistant to rifampin by developing mutations in the B subunit of RNA polymerase that render the enzyme unable to bind the antibiotic. The rapid selection of resistant mutants is the major limitation to the use of this antibiotic against otherwise-susceptible staphylococci and requires that it be used in combination with another antistaphylococcal agent.

### MULTIPLE ANTIBIOTIC RESISTANCE

The acquisition by one bacterium of resistance to multiple antibacterial agents is becoming increasingly common. The two major mechanisms are the acquisition of multiple unrelated resistance genes and the development of mutations in a single gene or gene complex that mediate resistance to a series of unrelated compounds. The construction of multiresistant strains by acquisition of multiple genes occurs by sequential steps of gene transfer and environmental selection in areas of high-level antimicrobial use. In contrast, mutations in a single gene can conceivably be selected in a single step. Bacteria that are multiresistant by virtue of the acquisition of new genes include hospital-associated gram-negative bacteria, enterococci, and staphylococci and community-acquired strains of salmonellae, gonococci, and pneumococci. Mutations that confer resistance to multiple unrelated antimicrobial agents occur in the genes encoding outer-membrane porins and efflux proteins of gram-negative bacteria. These mutations decrease bacterial intracellular and periplasmic accumulation ofb-lactams, quinolones, tetracycline, chloramphenicol, and trimethoprim. Multiresistant bacterial isolates pose increasing problems in U.S. hospitals; strains resistant to all available antibacterial chemotherapy have already been identified.

## PHARMACOKINETICS

The *pharmacokinetic profile* of an antibacterial agent refers to concentrations in serum and tissue versus time and reflects the processes of absorption, distribution, metabolism, and excretion. Important characteristics include peak and trough serum concentrations and mathematically derived parameters such as half-life, clearance, and distribution volume. Pharmacokinetic information is useful for estimating the appropriate antibacterial dose and frequency of administration, for adjusting dosages in patients with impaired excretory capacity, and for comparing one drug with another.*For further discussion of basic pharmacokinetic principles, see Chap. 70.*

### ABSORPTION

Data on absorption can refer to oral, intramuscular, or intravenous administration.

**Oral Administration** Most patients with infection are treated with oral antibacterial agents in the outpatient setting. Advantages of oral therapy over parenteral therapy include lower cost, generally fewer adverse effects (including complications of indwelling lines), and greater acceptance by patients. The percentage of an orally administered

antibacterial agent that is absorbed (i.e., the agent's *bioavailability*) ranges from as little as 10 to 20% (erythromycin and penicillin G) to nearly 100% (clindamycin, metronidazole, doxycycline, and trimethoprim-sulfamethoxazole). These differences in bioavailability are not clinically important as long as concentrations at the site of infection are sufficient to inhibit or kill the pathogen. However, therapeutic efficacy may be compromised when absorption is reduced as a result of physiologic or pathologic conditions (such as the presence of food for some drugs or the shunting of blood away from the gastrointestinal tract in patients with hypotension), drug interactions (such as that of quinolones and metal cations), or noncompliance. The oral route is usually used for patients with relatively mild infections in whom absorption is not thought to be compromised by the preceding conditions. In addition, the oral route can be used in more severely ill patients after they have responded to parenteral therapy.

**Intramuscular Administration** Although the intramuscular route of administration usually results in 100% bioavailability, it is not as widely used in the United States as the oral and intravenous routes, in part because of the pain often associated with intramuscular injections and the relative ease of intravenous access in the hospitalized patient. Intramuscular injection may be suitable for specific indications requiring an "immediate" and reliable effect (e.g., with long-acting forms of penicillin, including benzathine and procaine, and with single doses of ceftriaxone for uncomplicated gonococcal infection).

**Intravenous Administration** The intravenous route is appropriate when oral antibacterial agents are not effective against a particular pathogen, when bioavailability is uncertain, or when larger doses are required than are feasible with the oral route. After intravenous administration, bioavailability is 100%; serum concentrations are maximal at the end of the infusion. For many patients requiring long-term antimicrobial therapy, outpatient intravenous administration with the use of convenient portable pumps may be cost-effective and safe when oral therapy is not feasible. Alternatively, some oral antibacterial drugs such as fluoroquinolones are sufficiently active against Enterobacteriaceae to rival parenteral therapy; their use may allow the patient to return home from the hospital earlier or to avoid hospitalization entirely.

## DISTRIBUTION

To be effective, an antibacterial agent must exceed the minimal concentration required to inhibit bacterial growth (MIC;Chap. 121). Serum concentrations usually exceed the MIC for susceptible bacteria, but since most infections are extravascular, the antibiotic must also distribute to the site of the infection. Concentrations of most antibacterials in interstitial fluid are similar to free drug concentrations in serum. However, when the infection is located in a "protected" site where penetration is poor, such as cerebrospinal fluid (CSF), the eye, the prostate, or infected cardiac vegetations, high parenteral doses or local administration for prolonged periods may be required for cure. In addition, even though an antibacterial agent may penetrate to the site of infection, its activity may be antagonized by factors in the local environment, such as an unfavorable pH or inactivation by cellular degradation products. For example, since the activity of aminoglycosides is reduced at acidic pH, the acidic environment in many infected tissues may be partly responsible for the relatively poor efficacy of aminoglycoside monotherapy. In addition, the abscess milieu reduces the activity of many antibacterial

compounds, so that surgical drainage may be required for cure.

Most bacteria that cause human infections are located extracellularly. Intracellular pathogens such as *Legionella*, *Chlamydia*, *Brucella*, and *Salmonella* may persist or cause relapse if the antibacterial agent does not enter the cell. In general, b-lactams, vancomycin, and aminoglycosides penetrate cells poorly, whereas macrolides, tetracyclines, metronidazole, chloramphenicol, rifampin, trimethoprim-sulfamethoxazole, and quinolones penetrate cells well.

## METABOLISM AND ELIMINATION

Like other drugs, antibacterial agents are disposed of by hepatic elimination (metabolism or biliary elimination), by renal excretion in unchanged or metabolized form, or by a combination of the two processes. For most antibacterial drugs, metabolism leads to loss of in vitro activity, although some agents, such as cefotaxime, rifampin, and clarithromycin, have bioactive metabolites that may contribute to their overall efficacy.

The most practical application of knowing the mode of excretion of an antibacterial agent is adjustment of the dosage when elimination capability is impaired. Direct, nonidiosyncratic toxicity from antibacterial drugs most often results from failure to reduce the dosage appropriately in a patient with impaired elimination. For agents that are primarily cleared intact by glomerular filtration, drug clearance is linearly correlated with creatinine clearance. Unfortunately, for drugs whose elimination is primarily hepatic, no simple marker (such as serum creatinine) is useful for dosage adjustment in subjects with liver disease. Even in patients with severe hepatic disease, residual metabolic capability is usually sufficient to preclude accumulation and toxic effects. However, for drugs that undergo hepatic metabolism and have a narrow therapeutic index (such as chloramphenicol), alternative therapy may be warranted in patients with liver disease, since the technology for the monitoring of serum levels is not widely available.

# PRINCIPLES OF ANTIBACTERIAL CHEMOTHERAPY

The choice of an antibacterial compound for a particular patient and a specific infection involves more than just a knowledge of the agent's mechanism of action and pharmacokinetic profile. The basic tenets of chemotherapy, to be elaborated below, include the following: First, material containing the infecting organism(s) should be obtained before the start of treatment so that presumptive identification can be made by microscopic examination of stained specimens and the organism can be grown for definitive identification and susceptibility testing. Second, once the organism is identified and its susceptibility to antibacterial agents is determined, the regimen with the narrowest effective spectrum should be chosen. Third, the choice of antibacterial agent is guided by the pharmacokinetic and adverse-reaction profile of active compounds, the site of infection, the immune status of the host, and evidence of efficacy from well-performed clinical trials. Finally, if all other factors are equal, the least expensive antibacterial regimen should be chosen.

## SUSCEPTIBILITY OF BACTERIA TO ANTIBACTERIAL DRUGS IN VITRO

The determination of the susceptibility of the patient's infecting organism to a panel of appropriate antibacterial agents is an essential first step in devising a chemotherapeutic regimen. The details of susceptibility testing are discussed elsewhere (Chap. 121). Such testing is designed to estimate the susceptibility of a bacterial isolate to an antibacterial drug under standardized conditions that favor rapidly growing aerobic or facultative organisms and to assess bacteriostasis only. Specialized testing is required for the assessment of bactericidal antimicrobial activity; for the detection of resistance among such fastidious organisms as obligate anaerobes, *Haemophilus* spp., and pneumococci; and for the determination of resistance phenotypes with variable expression, such as resistance to methicillin or oxacillin among staphylococci.

## RELATIONSHIP OF PHARMACOKINETICS AND IN VITRO SUSCEPTIBILITY TO CLINICAL RESPONSE

The relationship between the report of susceptibility in vitro and the clinical pharmacokinetics of the antibacterial agent helps predict clinical response. Bacteria are usually considered to be *susceptible* to a drug if the achievable peak serum concentration exceeds theMIC by at least fourfold. The *breakpoint* is the concentration of the antibiotic that separates susceptible from resistant bacteria (Fig. 137-2). When a majority of the isolates of a given bacterial species are inhibited at concentrations below the breakpoint, the species is considered to be within the spectrum of the antibiotic (see "Choice of Antibacterial Therapy," below).

The pharmacodynamic profile of an antibiotic is the quantitative relationship among the time course of antibiotic concentrations in serum and tissue, in vitro susceptibility, and microbial response. Three pharmacodynamic parameters quantify these relationships: the ratio of the area under the curve (AUC) for the plasma concentration vs. time curve toMIC(AUC/MIC), the ratio of the maximal serum concentration to the MIC ($C_{max}$/MIC), and the time during a dosing interval that plasma concentrations exceed the MIC (*t* > MIC). The pharmacodynamic profile of an antibiotic class is characterized as either concentration dependent (fluoroquinolones, aminoglycosides), such that the increase in antibiotic concentration leads to a more rapid rate of bacterial death, or time dependent (b-lactams, vancomycin), such that the reduction in bacterial density is proportional to the time that concentrations exceed the MIC. For concentration-dependent antibiotics, the $C_{max}$/MIC or AUC/MIC ratio correlates best with the reduction in microbial density in vitro and in animal investigations. Dosing strategies attempt to maximize these ratios by the administration of a "large" dose relative to the MIC for anticipated pathogens, often at "long" intervals (relative to the serum half-life). Once-daily dosing of aminoglycoside antibiotics is the practical consequence of these relationships. In contrast, dosage strategies for time-dependent antibiotics emphasize the administration of sufficient doses at appropriate intervals to maintain serum concentrations above the MIC, typically for at least 40 to 50% of the dosing interval. The clinical implications of these relationships are in the early stages of investigation, but their elucidation should eventually result in more rational antibacterial regimens.

## STATUS OF THE HOST

Various host factors must be considered in the devising of antibacterial chemotherapy.

The host's antibacterial *immune function* is of importance, particularly as it relates to opsonophagocytic function. Since the major host defense against acute, overwhelming bacterial infection is the polymorphonuclear leukocyte, patients with neutropenia must be treated aggressively and empirically with bactericidal drugs for suspected infection (Chap. 85). Likewise, patients who have deficient humoral immunity (e.g., those with chronic lymphocytic leukemia and multiple myeloma) and individuals with surgical or functional asplenia (e.g., those with sickle cell disease) should be treated empirically for infections with encapsulated organisms, especially the pneumococcus.

*Pregnancy* increases the risk of toxicity of certain antibacterial drugs for the mother (e.g., the hepatic toxicity of tetracycline), affects drug disposition and pharmacokinetics, and -- because of the risk of fetal toxicity -- severely limits the choice of agents for treating infections. Certain antibacterials are contraindicated in pregnancy either because their safety has not been established or because they are known to be toxic. These agents include all fluoroquinolones, clarithromycin, erythromycin estolate (but not erythromycin base), and tetracyclines. Data on the safety of many other antibacterial drugs are limited, but these drugs may be used cautiously when there is no suitable alternative and the perceived benefit outweighs the risk. These agents include the aminoglycosides, azithromycin, clindamycin, imipenem, metronidazole, trimethoprim, and vancomycin. Chloramphenicol, nitrofurantoin, and the sulfonamides are contraindicated in the third trimester but can be used cautiously in the first two trimesters.

In patients with *concomitant viral infections*, the incidence of adverse reactions to antibacterial drugs may be unusually high. For example, persons with infectious mononucleosis and those infected with HIV may react more often to ampicillin and folic acid synthesis inhibitors, respectively.

In addition, the patient's age, sex, racial heritage, and excretory status all determine the incidence and type of side effects that can be expected with certain antibacterial agents.

**SITE OF INFECTION**

The location of the infected site may play a major role in the choice and dose of antimicrobial drug. Patients with suspected *meningitis* should receive drugs that can cross the blood-CSFbarrier; in addition, because of the relative paucity of phagocytes and opsonins at the site of infection, the agents should be bactericidal. Chloramphenicol, one of the standard drugs used in the treatment of meningitis, is bactericidal for common organisms causing meningitis (i.e., meningococci, pneumococci, and *Haemophilus influenzae*, but *not* enteric gram-negative bacilli), is highly lipid-soluble, and enters the CSF well. However,b-lactams, the mainstay of therapy for most of these infections, do not normally reach high levels in CSF. Their efficacy is based on the increased permeability of the blood-brain and blood-CSF barriers to hydrophilic molecules during inflammation and the extreme susceptibility of most infectious organisms to even small amounts of b-lactam drug.

The vegetation, which is the major site of infection in *bacterial endocarditis*, is also a focus that is protected from normal host-defense mechanisms. Antibacterial therapy needs to be bactericidal, with the selected agent administered parenterally over a long

period and at a dose that produces serum levels at least eight times higher than the minimal bactericidal concentration (MBC) for the infecting organism. Likewise, *osteomyelitis* involves a site that is somewhat resistant to opsonophagocytic removal of infecting bacteria; furthermore, avascular bone (sequestrum) represents a foreign body that thwarts normal host-defense mechanisms. *Chronic prostatitis* is exceedingly difficult to cure because most antibiotics do not penetrate the nonfenestrated capillaries serving the prostate, especially when acute inflammation is absent. Drugs that are "ion trapped" after entering prostatic tissue, such as trimethoprim and fluoroquinolones, may be uniquely effective because of this mechanism. *Intraocular infections*, especially endophthalmitis, are difficult to treat because drug penetration into the vitreous from blood is hindered by retinal capillaries lacking fenestration. Inflammation does little to disrupt this barrier. Thus, direct injection into the vitreous is necessary in many cases. Antibiotic penetration into *abscesses* is usually poor. Even when an antibiotic does penetrate into the abscess, local conditions, such as low pH or the presence of enzymes that hydrolyze the drug, may antagonize its activity.

In contrast, *urinary tract infections*, when confined to the bladder, are relatively easy to cure, in part because of the higher concentration of most antibiotics in urine than in blood. Since blood is the usual reference fluid in defining susceptibility, even organisms found to be "resistant" to achievable serum concentrations may be susceptible to achievable urine concentrations. For drugs that are used only for the treatment of urinary tract infections, such as nitrofurantoin and methenamine salts, achievable urine concentrations are used to determine susceptibility.

## COMBINATION CHEMOTHERAPY

One of the tenets of antibacterial chemotherapy is that if the infecting bacterium has been identified, the most specific chemotherapy possible should be used. The use of a single agent with a narrow spectrum of activity against the pathogen diminishes the alteration of normal flora and thus limits the overgrowth of resistant nosocomial organisms (e.g., *Candida albicans*, enterococci, *Clostridium difficile*, or methicillin-resistant staphylococci), avoids the potential toxicity of multiple-drug regimens, and reduces cost. However, certain circumstances call for the use of more than one antibacterial agent. These are summarized below.

1. *Prevention of the emergence of resistant mutants.* Spontaneous mutations occur at a detectable frequency in certain genes encoding the target proteins for some antibacterial agents. The use of these agents can eliminate the susceptible population, select out resistant mutants at the site of infection, and result in the failure of chemotherapy. Resistant mutants are usually selected when theMIC of the antibacterial agent for the infecting bacterium is close to achievable levels in serum or tissues and/or when the site of infection limits the access or activity of the agent. Among the most common examples are rifampin for staphylococci, imipenem for *Pseudomonas*, and ciprofloxacin for staphylococci and *Pseudomonas*. Small-colony variants of staphylococci resistant to aminoglycosides also emerge during monotherapy with these antibiotics. A second antibacterial agent with a mechanism of action different from that of the first is added to prevent the emergence of these resistant mutants (e.g., imipenem plus an aminoglycoside for systemic *Pseudomonas* infections). However, since resistant mutants have emerged following combination chemotherapy, this

approach is not uniformly successful.

2. *Synergistic or additive activity.* Against some bacteria, two or more agents are clearly more active than one; whether or not this is the case is usually judged on the basis of testing in vitro. Synergistic or additive activity involves a lowering of theMIC orMBC of each or all of the drugs tested in combination against a specific bacterium. In *synergy*, *each* agent is more active when combined with a second drug than it would be alone, and the drugs' combined activity is therefore greater than the sum of the individual activities of each drug. In an *additive relationship*, the combined activity of the drugs is equal to the sum of their individual activities. Among the best examples of a synergistic or additive effect, confirmed both in vitro and by animal studies, are the enhanced bactericidal activities of certainb-lactam/aminoglycoside combinations against enterococci, viridans streptococci, and *P. aeruginosa*. The synergistic or additive activity of these combinations has also been demonstrated for selected isolates of enteric gram-negative bacteria and staphylococci. The combination of trimethoprim and sulfamethoxazole has synergistic or additive activity against many enteric gram-negative bacteria. Most other antimicrobial combinations display indifferent activity (i.e., the combination is *no better* than the more active of the two agents alone), and some combinations (e.g., penicillin plus tetracycline against pneumococci) may be antagonistic (i.e., the combination is *worse* than either drug alone).

3. *Therapy directed against multiple potential pathogens.* For certain infections, either a mixture of pathogens is suspected or the patient is desperately ill with an as-yet-unidentified infection (see "Empirical Therapy," below). In these situations, the most important of the likely infecting bacteria must be covered by therapy until culture and susceptibility results become available. Examples of the former infections are intraabdominal or brain abscesses and infections of limbs in diabetic patients with microvascular disease. The latter situations include fevers in neutropenic patients, acute pneumonia from aspiration of oral flora by hospitalized patients, and septic shock or sepsis syndrome.

## EMPIRICAL THERAPY

In certain situations, antibacterial therapy is begun before a specific bacterial pathogen has been identified. The choice of agent is guided by the results of studies identifying the usual pathogens at that site or in that clinical setting, by pharmacodynamic considerations, and by the resistance profile of the expected pathogens in a particular hospital or geographic area. Situations in which empirical therapy is appropriate include the following:

1. *Life-threatening infection*. Any suspected bacterial infection in a patient with a life-threatening illness should be treated presumptively. Therapy is usually begun with more than one agent and is later tailored to a specific pathogen if one is eventually identified.

2. *Treatment of infections in unhospitalized patients with no cultures performed*. In many situations, it is appropriate to treat non-life-threatening infections without obtaining cultures. These situations include outpatient infections such as community-acquired cases of pneumonia, cystitis, cellulitis or local wound infection, sinusitis, otitis, urethritis,

and prostatitis. However, if any of these infections recurs or fails to respond to initial therapy, every effort should be made to obtain cultures to guide re-treatment.

## CHOICE OF ANTIBACTERIAL THERAPY

The antibacterial spectrum of specific agents and the infections for which they represent the treatment of choice are detailed below. No attempt has been made to include all the potential situations in which antibacterial agents may be used. A more detailed discussion of specific bacteria and infections that they cause can be found elsewhere in this volume.

### b-LACTAMS (Table 137-2)

All *penicillins* (except for the semisynthetic, penicillinase-resistant antistaphylococcal agents) are hydrolyzed byb-lactamases and are ineffective against isolates that produce these enzymes. Penicillin G has a spectrum that includes spirochetes (*Treponema pallidum*, *Borrelia*, and *Leptospira*), streptococci (groups A and B, viridans, and *Streptococcus pneumoniae*), enterococci, most *Neisseria* spp., a few staphylococci, many fastidious oral bacteria (including many *Porphyromonas* and *Prevotella* spp., streptococci, *Actinomyces*, and *Fusobacterium*), *Clostridium* spp. (except *C. difficile*), *Pasteurella multocida*, *Erysipelothrix rhusiopathiae*, and *Streptobacillus moniliformis*. However, penicillin G resistance is widespread among staphylococci; is increasing rapidly among gonococci, enterococci, and pneumococci; and is emerging among meningococci, viridans streptococci, and oral anaerobes such as *Porphyromonas* and *Prevotella*. Penicillin G is the *drug of choice* for syphilis, yaws, leptospirosis, group A and B streptococcal infections, actinomycosis, oral and periodontal infections, meningococcal meningitis and meningococcemia, viridans streptococcal endocarditis, clostridial myonecrosis, tetanus, anthrax, rat-bite fever, *P. multocida* infections, and erysipeloid (*E. rhusiopathiae*).

Ampicillin extends the spectrum of penicillin G to some gram-negative rods. It is active against some isolates of *Escherichia coli*, *Proteus mirabilis*, *Salmonella*, *Shigella*, and *H. influenzae* and is one of the *drugs of choice* for susceptible organisms causing urinary tract infections, salmonellosis, *H. influenzae* meningitis and epiglottitis, and *Listeria monocytogenes* meningitis. High rates of resistance have lessened its value as empirical therapy in some situations. For example, more than 80% of isolates of *E. coli* and *P. mirabilis* are resistant in some hospitals, as are 10 to 30% of isolates of *H. influenzae*; moreover, in some outbreaks of infection due to salmonellae, all isolates are ampicillin-resistant.

The *penicillinase-resistant penicillins* are used solely for the treatment of staphylococcal infections and are the *drugs of choice* for systemic or deep staphylococcal infections caused by susceptible organisms. Unfortunately, on average, approximately 30% of *S. aureus* isolates and more than 60% of coagulase-negative staphylococcal isolates acquired in U.S. hospitals are resistant to these agents (i.e., methicillin-resistant). The spectrum of these agents also includes most of the same gram-positive bacteria that are susceptible to penicillin G.

The spectrum of the *antipseudomonal penicillins* includes the bacteria covered by

ampicillin as well as some additional nonpseudomonal enteric gram-negative bacilli. For example, piperacillin is active against many indole-positive *Proteus*, *Enterobacter*, *Klebsiella*, *Providencia*, and *Serratia* spp. However, the susceptibility of these penicillins tob-lactamase markedly limits their utility as empirical therapy when infections caused by gram-negative enteric organisms are suspected. The major use of these compounds is in the treatment of proven or suspected infections with *P. aeruginosa* and *Acinetobacter*, for which they are among the *drugs of choice*. Their relative antipseudomonal activities can be ranked as follows: piperacillin >mezlocillin/ticarcillin >carbenicillin.

The addition of*b-lactamase inhibitors* (clavulanic acid, sulbactam, or tazobactam) to ampicillin, amoxicillin, ticarcillin, or piperacillin extends the spectrum of these agents to include many organisms that are resistant by virtue of b-lactamase production. These organisms include *E. coli*, *Klebsiella* spp., all *Proteus* spp., *H. influenzae*, *Moraxella catarrhalis*, *Providencia* spp., and *Bacteroides* spp. Such combinations are also active against staphylococci that produce b-lactamase but are not methicillin-resistant. However, the efficacy of these combinations in serious staphylococcal infections has not been adequately proven. Furthermore, *Enterobacter*, *Pseudomonas*, *Acinetobacter*, and various enteric gram-negative isolates either produceb-lactamases not inhibited by these compounds or develop resistance attributable to non-b-lactamase-mediated mechanisms.

The *first-generation cephalosporins* have a spectrum that includes penicillinase-producing, methicillin-susceptible staphylococci and streptococci. While these drugs may be used when infections with gram-positive bacteria are suspected, they are *not* the drugs of choice for such infections. They have excellent activity against many isolates of *E. coli*, *Klebsiella pneumoniae*, and *P. mirabilis* and are among the *drugs of choice* in presumptive therapy for community-acquired urinary tract infections. They have no activity against *Bacteroides fragilis*, enterococci, methicillin-resistant staphylococci, *Pseudomonas*, *Acinetobacter*, *Enterobacter*, indole-positive *Proteus*, and *Serratia* and poor activity against *H. influenzae*.

The *parenteral second-generation cephalosporins* extend the gram-negative spectrum of first-generation compounds. The various second-generation agents have differing activities. Cefuroxime and cefamandole retain activity against gram-positive cocci and are also active against *H. influenzae*, *Neisseria*, some *Enterobacter* isolates, and indole-positive *Proteus* but exhibit poor activity against *B. fragilis*. Cefoxitin and cefotetan have reasonably good activity against *B. fragilis*, but cefotetan is less effective against some other *Bacteroides* spp. (Chaps. 130 and167). Both of the latter drugs display poor activity against gram-positive cocci and *Enterobacter*. No second-generation cephalosporin is active against *Pseudomonas* or *Acinetobacter*.

*Oral second-generation cephalosporins* have fair activity against gram-positive cocci and *H. influenzae* and are widely used in outpatient therapy for otitis media, sinusitis, and lower respiratory tract infections, although cheaper agents that are equally effective are preferable. Cefixime, cefuroxime axetil, and cefpodoxime are among the *drugs of choice* for single-dose treatment of gonococcal urethritis.

*Third-generation cephalosporins* all have a broad spectrum of activity against enteric

gram-negative rods and are especially useful for treating hospital-acquired infections caused by multiresistant organisms. In addition, ceftazidime and cefepime have excellent antipseudomonal activity. The other third-generation cephalosporins have poor antipseudomonal activity. Since resistance to third-generation cephalosporins is increasing among all nosocomial gram-negative rods, the use of these agents should be guided by susceptibility testing. The gram-positive spectrum of the third-generation cephalosporins is variable. All are less active than first-generation cephalosporins against methicillin-susceptible staphylococci; ceftazidime has the least antistaphylococcal activity of this group. However, ceftriaxone, ceftizoxime, and cefotaxime have excellent activity against streptococci, especially *S. pneumoniae*. Ceftazidime is not recommended for treatment of streptococcal infections.

Because of its excellent gram-negative spectrum; its activity against *Haemophilus*, many *S. pneumoniae* strains, and penicillin-resistant *Neisseria*; its long serum half-life; and its high serum andCSFlevels, ceftriaxone has become one of the *drugs of choice* for empirical therapy for bacterial meningitis (except that caused by *Listeria* and by highly penicillin-resistant pneumococcal strains), all gonococcal infections, salmonellosis, and typhoid fever. The third-generation cephalosporins are among the *drugs of choice* for nonpseudomonal hospital-acquired pneumonia. Cefepime is more resistant to chromosomal b-lactamase produced by *Enterobacter* spp. than are other third-generation cephalosporins. Third-generation cephalosporins have poor activity against *Bacteroides* and no activity against methicillin-resistant staphylococci, *Enterococcus*, *Acinetobacter*, or *Stenotrophomonas*.

The *carbapenems* currently available in the United States are imipenem and meropenem. Imipenem is marketed in combination with the renal dipeptidase inhibitor cilastatin, which enables imipenem to escape renal inactivation and thus to reach higher urinary levels. Imipenem and meropenem have excellent activity in vitro against virtually all bacterial pathogens except *Stenotrophomonas*, methicillin-resistant staphylococci, and *E. faecium*. Limitations to their use are their relatively low blood levels, short serum half-life, and high cost. Imipenem has dose-related central nervous system side effects that appear to be less frequent with meropenem. Resistance to imipenem and meropenem is a problem only among nosocomial isolates of *P. aeruginosa*, approximately 20% of which are resistant. Because of their broad spectrum, carbapenems can be used as empirical therapy for serious nosocomial infections thought to be caused by multiple bacterial species or multiresistant organisms. Imipenem and meropenem are often used to treat hospital-acquired infections caused by *Enterobacter* spp. because these organisms produce inducibleb-lactamases that inactivate third-generation cephalosporins but not the carbapenems. The latter antibiotics are often held in reserve as therapy for nosocomial infections due to gram-negative pathogens resistant to third-generation cephalosporins.

The only *monobactam* currently available is aztreonam. This antibiotic has a spectrum limited to facultative gram-negative enteric bacilli. It has no activity against any gram-positive or anaerobic bacterium. Its gram-negative spectrum is similar to that of ceftazidime, with equally good activity against *Pseudomonas*. Its primary advantages are its theoretical ability to preserve the normal gram-positive and anaerobic flora and the lack of cross-reactive immediate hypersensitivity in patients who have had this type of reaction to otherb-lactam antibiotics.

## VANCOMYCIN

The spectrum of vancomycin is limited to gram-positive cocci, especially enterococci, streptococci, and staphylococci. Vancomycin serves as second-line therapy for most gram-positive bacterial infections but is the *drug of choice* for infections caused by methicillin-resistant staphylococci or *Corynebacterium jeikeium* and for serious infections in penicillin-allergic patients. Given orally (a route by which it is not absorbed), vancomycin can be used to treat antibiotic-associated pseudomembranous colitis caused by *C. difficile* in patients who have failed to respond to metronidazole, the *drug of choice*. Vancomycin has also been recommended as initial empirical therapy for presumed pneumococcal meningitis because of increasing pneumococcal resistance to penicillins and cephalosporins. Resistance to vancomycin is increasing rapidly among isolates of *E. faecium* in large hospitals, particularly in areas of high vancomycin use. In addition, *S. aureus* isolates with reduced susceptibility to vancomycin have now been detected. Because of the growing threat of vancomycin-resistant enterococci and the potential for increasing resistance among staphylococci, a national advisory committee has established guidelines for appropriate and limited use of this antibiotic.

## AMINOGLYCOSIDES

The aminoglycosides are rapidly bactericidal in vitro at low concentrations, with activity limited to facultative gram-negative bacteria and staphylococci. They have no activity against anaerobic bacteria and are not effective in environments that are acidic or have a low oxygen tension. However, their spectrum includes virtually all gram-negative bacteria that are not strict anaerobes, and they are among the *drugs of choice* for any suspected gram-negative bacteremic infection, particularly in neutropenic patients. Aminoglycosides are synergistically bactericidal in combination with a penicillin for the treatment of staphylococcal, enterococcal, or viridans streptococcal endocarditis and are usually combined with ab-lactam antibiotic for the treatment of gram-negative bacteremia. Aminoglycosides are also among the *drugs of choice* for severe infections of the upper urinary tract. The major limitations to use of aminoglycosides are their renal and otic toxicity, their diminished activity at certain sites of infection (e.g., abscesses and the central nervous system), and the resistance of target bacteria. Among the available agents, gentamicin is generally preferred because of its low cost; however, tobramycin has slightly greater activity against *P. aeruginosa*, and amikacin retains activity against many tobramycin- and gentamicin-resistant gram-negative bacteria because it is inactivated by fewer aminoglycoside-modifying enzymes. Streptomycin is still one of the *drugs of choice* in initial therapy for tularemia, plague, glanders, and brucellosis and is a second-line agent for the treatment of tuberculosis.

## MACROLIDES

Erythromycin has broad-spectrum activity against gram-positive bacteria, with additional activity against *Legionella*, *Mycoplasma*, *Campylobacter*, and some *Chlamydia* isolates. It is the *drug of choice* for infections due to *Legionella*, *Campylobacter*, and *Mycoplasma* and is among the *drugs of choice* for community-acquired pneumococcal pneumonia and group A streptococcal pharyngitis in penicillin-allergic patients. However, resistance to erythromycin among group A streptococci and pneumococci is increasing

dramatically in some areas. Erythromycin also appears to be one of the *drugs of choice* for infections caused by the agent of bacillary angiomatosis (*Bartonella henselae*) in immunocompromised patients. The newer macrolides clarithromycin and azithromycin have an antibacterial spectrum similar to that of erythromycin in vitro. However, azithromycin has greater activity against *Chlamydia*. Clarithromycin, in combination with a proton pump inhibitor, has been designated a *drug of choice* for the treatment of gastric infections due to *Helicobacter pylori* (gastritis, gastric and duodenal ulcers). Both azithromycin and clarithromycin are active against nontuberculous mycobacteria, and both appear to have fewer gastrointestinal side effects than does erythromycin.

## LINCOSAMIDES

The only lincosamide used in the United States is clindamycin. It shares the gram-positive coccal spectrum of erythromycin but is more active, in some cases showing bactericidal activity, against susceptible staphylococci. However, resistance among staphylococci and some streptococci, mediated by the same genes responsible for macrolide resistance, limits clindamycin's usefulness against gram-positive cocci. In general, all staphylococci resistant to erythromycin should be considered resistant to clindamycin regardless of the results of in vitro susceptibility testing. However, at least half of the streptococci resistant to erythromycin are truly susceptible to clindamycin. In these bacteria, resistance is mediated by a drug-efflux pump that removes macrolides but not lincosamides. Despite increasing resistance, clindamycin remains useful for most anaerobic infections because of its broad spectrum of activity against both gram-positive and -negative strict anaerobes. It is also a *drug of choice* for the treatment of severe, invasive group A streptococcal infections. In contrast, clindamycin, like erythromycin, has no clinically significant activity against facultative gram-negative enteric bacilli. Appropriate use is limited only by resistance or the development of pseudomembranous colitis, the major serious side effect of this drug.

## CHLORAMPHENICOL

Chloramphenicol has a broad spectrum of activity against gram-positive and -negative bacteria, although plasmid-mediated resistance has diminished its effective spectrum. This antibiotic is rarely used in adult infections because of the rare idiosyncratic side effect of irreversible bone-marrow aplasia and the availability of other agents with similar activity. It remains one of the *drugs of choice* for the treatment of typhoid fever and plague and is still useful for the treatment of brucellosis and both pneumococcal and meningococcal meningitis in penicillin-allergic patients.

## TETRACYCLINES

Tetracyclines have a broad spectrum of bacteriostatic activity against gram-positive and -negative bacteria and are widely used in a variety of community-acquired infections. These agents are among the *drugs of choice* for chronic bronchitis, granuloma inguinale, brucellosis (with streptomycin), tularemia, glanders, melioidosis, spirochetal infections caused by *Borrelia* (Lyme disease and relapsing fever; doxycycline), infections caused by *Vibrio vulnificus*, some *Aeromonas* infections, infections due to *Stenotrophomonas* (minocycline), plague, and ehrlichiosis (doxycycline). The tetracyclines are also used in penicillin-allergic patients for the treatment of

leptospirosis, syphilis, actinomycosis, and skin and soft-tissue infections caused by gram-positive cocci. They are among the *drugs of choice* for infections due to chlamydiae (doxycycline), rickettsiae, and ehrlichiae and for granulomatous skin infection due to *Mycobacterium marinum* (minocycline). Doxycycline is also among the drugs recommended for the treatment of community-acquired pneumonia.

## SULFONAMIDES AND TRIMETHOPRIM

The folic acid synthesis inhibitors have a broad spectrum of bacteriostatic activity individually; in combination, they can be bactericidal against facultative gram-negative bacteria and staphylococci. The fixed combination of sulfamethoxazole and trimethoprim, the major folic acid synthesis inhibitors used in therapy for bacterial infections, has modest activity against some streptococci and no activity against strict anaerobes. However, resistance to the combination of sulfamethoxazole and trimethoprim is common among methicillin-resistant staphylococci and penicillin-resistant pneumococci and is increasing among *E. coli* strains that cause urinary tract infections. The individual sulfonamides are rarely used in the treatment of bacterial infections but are among the *drugs of choice* for the treatment of nocardial infections, leprosy (dapsone, a sulfone), and toxoplasmosis (sulfadiazine). Although increasing resistance has been reported among gram-negative organisms, trimethoprim-sulfamethoxazole remains one of the *drugs of choice* for the treatment of uncomplicated urinary tract infections (except for those caused by enterococci) and is widely used in the treatment of otitis media. It can be used in therapy for upper respiratory tract infections in which *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* is suspected; for gonococcal and meningococcal infections; for chancroid; and for infections thought to be caused by *Aeromonas*, *Stenotrophomonas*, *Burkholderia cepacia*, *Acinetobacter*, and *Yersinia enterocolitica*. For nosocomial infections due to *Stenotrophomonas*, trimethoprim-sulfamethoxazole is the *drug of choice*.

## FLUOROQUINOLONES

The fluoroquinolones have excellent activity against most facultative gram-negative rods and variable activity against gram-positive cocci; only trovafloxacin is active against obligate anaerobes. The quinolones are the oral agents with greatest activity against *P. aeruginosa*; ciprofloxacin is the most active against this species. All the quinolones except norfloxacin are well absorbed orally; ciprofloxacin, levofloxacin, trovafloxacin, and ofloxacin are also administered as intravenous formulations. The quinolones are among the *drugs of choice* for urinary tract infections, bacterial gastroenteritis, community-acquired pneumonia, and enteric fever and may be useful in therapy for serious hospital-acquired infections caused by gram-negative organisms. While older quinolones (ciprofloxacin, ofloxacin, and norfloxacin) have limited activity against gram-positive bacteria, the newer quinolones have an expanded spectrum of activity against gram-positive cocci, including staphylococci (both methicillin-susceptible and methicillin-resistant) and streptococci (especially *S. pneumoniae*). However, because of the potential for development of severe liver toxicity, it has been recommended that trovafloxacin use be limited to hospitalized patients with serious or life-threatening infections. Quinolones can also be used as prophylaxis for persons at risk for meningococcal meningitis. However, rapid expansion in the use of quinolones should be coupled with a consideration of the potential for development of resistance among all

bacteria targeted by these drugs.

### RIFAMPIN

Rifampin has been used in combinations for the treatment of serious infections due to methicillin-resistant staphylococci (e.g., coagulase-negative staphylococcal foreign-body infections). Because the spontaneous selection of rifampin-resistant mutants occurs rapidly, rifampin should never be used alone in the treatment of staphylococcal infections. Rifampin is also used for chemoprophylaxis in persons at risk of meningococcal meningitis and for the treatment of *Legionella* pneumonia.

### METRONIDAZOLE

Metronidazole has a spectrum limited to anaerobic bacteria. It is one of the *drugs of choice* for the treatment of any abscess in which the involvement of obligate anaerobes is suspected (e.g., lung, brain, or intraabdominal abscesses) because of its spectrum and its ability to penetrate into the area of infection. Other antibacterial agents should be used in combination with metronidazole if facultative and aerobic pathogens are also thought to be involved. Metronidazole is the *drug of choice* for the treatment of bacterial vaginosis and antibiotic-associated pseudomembranous colitis.

### URINARY TRACT ANTISEPTICS

Urinary tract antiseptics are active only in the lower urinary tract and cannot be used for the treatment of upper urinary tract or systemic infections. Their activity is limited to susceptible gram-negative enteric bacteria. The available agents in this category include nitrofurantoin and methenamine salts.

### TOPICAL ANTIBACTERIAL AGENTS

Mupirocin is available only as a topical preparation for use against staphylococci and streptococci. Its major applications are for impetigo and eradication of the staphylococcal carrier state. It is the *drug of choice* for the elimination of nasal carriage of both methicillin-susceptible and methicillin-resistant staphylococci. Unfortunately, the emergence of resistance is limiting its usefulness in some hospitals.

Although their efficacy has never been well documented, topical preparations that include sulfonamides, polymyxin B, neomycin, bacitracin, gramicidin, and novobiocin in a variety of combinations are widely used as eye drops, irrigation solutions, and ointments for superficial skin infections.

## ADVERSE REACTIONS

Adverse drug reactions are frequently classified by mechanism as either dose-related ("toxic") effects or unpredictable reactions. Unpredictable reactions are further categorized as either idiosyncratic or allergic. Dose-related reactions include aminoglycoside-induced nephrotoxicity, penicillin-induced seizures, and vancomycin-induced anaphylactoid reactions. Many of these reactions can be avoided by reducing dosage, limiting the duration of therapy, or reducing the frequency or rate of

administration. Adverse reactions to antibacterial agents are a common cause of morbidity, requiring alteration in therapy and additional expense, and they occasionally result in death. The elderly, often those with the more severe infections, may be especially prone to certain adverse reactions.*For further discussion of adverse drug reactions, see Chap. 71.*

## b-LACTAMS

The therapeutic index for b-lactam antibiotics is broad, and dose-related adverse reactions are uncommon and largely preventable. The greatest concern is allergic reactions. All types can occur, including anaphylaxis (type 1, hypersensitivity reactions), nephritis and Coombs-positive hemolytic anemia (type 2, cytotoxic reactions), drug fever and serum sickness (type 3, immune-complex formation), contact dermatitis (type 4, cell-mediated effects), and maculopapular eruption (type 5, idiopathic reactions). Approximately 1 to 4% of treatment courses result in an allergic reaction, and approximately 0.004 to 0.015% of treatment courses result in anaphylaxis. Fewer than half the patients who claim an allergy to penicillin react to skin testing with the major and minor determinants (penicilloyl-polylysine and benzylpenicillin degradation products, respectively); those with negative skin tests only rarely react adversely to subsequent therapeutic doses. Generally, a suitable alternative to b-lactams is available for patients who have a severe allergy, and penicillin desensitization can be carefully undertaken if there is no suitable alternative. A small proportion (<2%) of persons who are allergic to penicillin react similarly when a cephalosporin is administered; thus, cephalosporins are contraindicated in patients with a history of an immediate reaction to penicillin, although they are often used in patients with a history of mild reactions. The same precaution applies to imipenem, but aztreonam is antigenically distinct and can be administered safely to the penicillin-allergic patient.

Other reactions thought to have an allergic basis include nephritis (associated with methicillin and occasionally nafcillin), hepatitis (related to oxacillin), leukopenia (following high doses of most b-lactams administered for prolonged periods), and severe skin rashes (toxic epidermal necrolysis and Stevens-Johnson syndrome). These reactions are not IgE-mediated, and skin testing is not predictive of their occurrence. For unclear reasons, most patients who have infectious mononucleosis develop a rash when given ampicillin or amoxicillin.

Miscellaneous reactions tob-lactams include gastrointestinal side effects ranging in severity from mild diarrhea (5 to 10%) to pseudomembranous colitis (<1%). Although the probability of antibiotic-associated colitis is low, a large number of cases occur becauseb-lactams are so commonly prescribed. Drugs excreted to a large extent through the bile, such as ampicillin and ceftriaxone, may be especially prone to cause diarrhea. The addition of clavulanic acid to amoxicillin further increases the frequency of diarrhea. Ceftriaxone, because of extremely high concentrations in bile, can cause "sludging" in the gallbladder and occasionally produces symptoms compatible with acute cholecystitis.

In high doses -- and most often in patients with renal impairment who receive an excessive dose -- penicillins (especially ticarcillin and penicillin G) can cause bleeding from impaired platelet aggregation. Ticarcillin is a disodium salt and in high doses can

cause hypokalemia and fluid overload.

Seizures are occasionally observed with b-lactams, especially penicillin G and imipenem. This reaction is most common when excessive doses relative to renal function are administered or when the patient has a history of seizures.

## VANCOMYCIN

When vancomycin was first used clinically in 1956, local intolerance at the infusion site was common, as were systemic reactions, including ototoxicity and nephrotoxicity. Current formulations are of higher purity and, when proper dosage guidelines are followed, are very safe, although phlebitis can still be troublesome. The most common adverse reaction is called *red man syndrome* and is characterized by pruritus, flushing, and erythema of the head and upper torso. This anaphylactoid reaction usually follows the first dose, is dependent on dose size and infusion time, and results from vancomycin-induced release of histamine. The reaction is usually mild in adult patients who receive 1 g over 60 min and diminishes with repeated doses. If vancomycin is mistakenly given as a bolus, severe hypotension may result. In unusually sensitive patients, extending the infusion time or administering $H_1$receptor antagonists is usually effective in preventing this reaction or reducing its severity. Patients with this reaction must not be mislabeled as having an allergy to vancomycin, since vancomycin may be the only effective treatment for certain infections, such as those due to methicillin-resistant staphylococci.

Nephrotoxicity from vancomycin is mild and occurs in fewer than 5% of patients. Although some data suggest that aminoglycosides and vancomycin are synergistically nephrotoxic, this point is difficult to prove, and the simultaneous use of these agents should not be avoided if clinically indicated, as in the treatment of enterococcal endocarditis in penicillin-allergic patients.

Ototoxicity from vancomycin is rare as long as doses are appropriately reduced in patients with renal insufficiency. Other uncommon adverse reactions include leukopenia, skin rashes, and true allergy. Serum concentrations of vancomycin are of little use in predicting toxicity but may be of value in selecting dosages for patients with unstable renal function.

## AMINOGLYCOSIDES

Aminoglycoside antibiotics have a narrow therapeutic index. The two most common adverse reactions are nephrotoxicity and ototoxicity. Rarely, respiratory depression is observed. Nephrotoxicity results from accumulation of the aminoglycoside in the peritubular space, with damage to the proximal tubule and a corresponding reduction in the glomerular filtration rate. The incidence of nephrotoxicity, defined as a >0.5% increase over baseline in the serum creatinine level, is approximately 5 to 10% among adult patients who receive therapy for 10 to 14 days. However, many cofactors also influence the frequency of toxicity, such as extremes of age (toxicity is uncommon among children, more common among the elderly), concomitant drug therapy, and hydration status. Nephrotoxicity is manifested clinically by a gradual rise in serum creatinine levels after a few days of therapy and is reversible if the dosage is reduced or

treatment is discontinued. Serum creatinine levels should be monitored every 3 to 5 days or more often if changes are seen. There is not an important difference among the most useful agents (gentamicin, tobramycin, and amikacin) in terms of the frequency of nephrotoxicity; streptomycin is a rare cause of nephrotoxicity. Some data suggest that once-daily administration may cause less nephrotoxicity.

Ototoxicity from aminoglycoside therapy presents as either auditory or vestibular damage. Since the aminoglycosides can destroy hair cells in the inner ear, ototoxicity may be permanent. The risk of ototoxicity increases with prolonged therapy, higher serum concentrations (especially in patients with renal impairment), hypovolemia, and concurrent treatment with other ototoxins, especially ethacrynic acid. Clinically apparent ototoxicity, manifested by diminished acuity or vestibular imbalance, is uncommon (probably occurring in<1% of cases) when the duration of therapy is kept to a minimum. With more sensitive monitoring (e.g., audiograms), asymptomatic high-tone hearing loss is more commonly noted. There are no clinically important differences among the aminoglycosides in the overall frequency of ototoxicity.

Neuromuscular depression from aminoglycosides is caused by reduced acetylcholine activity at postsynaptic membranes and can result in rare but severe respiratory depression. Risk factors include hypocalcemia, peritoneal administration, use of neuromuscular blockers, and preexisting respiratory depression. This complication can be largely avoided if the aminoglycoside is administered intravenously over 30 min or by intramuscular injection; if respiratory depression occurs, it is reversed by the administration of calcium.

Fear of toxicity should not prevent the use of aminoglycosides for a legitimate indication, since toxicity is usually mild and reversible. The value of measuring serum concentrations is controversial; these measurements are usually unnecessary when the patient is receiving once-daily therapy.

## MACROLIDES

Serious adverse reactions to the macrolide antibiotics are very rare. Gastrointestinal effects, such as burning, nausea, and vomiting, are the most common adverse reactions to the macrolides; depending on dosage, these reactions may occur in up to 50% of patients, occasionally requiring early discontinuation of therapy. The mechanism is thought to be the binding of erythromycin to motilin receptors, with a consequent increase in gastrointestinal motility. Gastrointestinal side effects appear equally common for all the oral formulations and also occur with intravenous administration. Clarithromycin and azithromycin are better tolerated than erythromycin, although gastrointestinal distress is still their most common adverse effect.

Less common reactions include hepatotoxicity and ototoxicity. Hepatotoxicity is a rare, nonfatal complication that is usually associated with erythromycin estolate and presents as an allergic cholestatic jaundice. Ototoxicity is rare after oral administration but may occur in a dose-dependent pattern in up to 20% of adults who receive intravenous erythromycin (4 g/d) and have audiograms performed. Ototoxicity is usually reversible and mild. Allergic cutaneous reactions are observed in rare cases.

## LINCOSAMIDES

The most common adverse effect of clindamycin is gastrointestinal distress. Diarrhea has been reported in up to 20% of patients and pseudomembranous colitis in 0.01 to 10%. The mechanism of pseudomembranous colitis is production of a toxin by *C. difficile* (Chap. 145). *C. difficile* colonizes the gastrointestinal tract and may produce a toxin when the normal flora is suppressed by clindamycin and other antibiotics, especiallyb-lactams. This toxin causes mucosal damage that results in cramps, pain, and diarrhea that may be bloody. Pseudomembranous colitis may follow both intravenous and oral administration and may not become manifest until after completion of therapy. Oral metronidazole or oral vancomycin is effective in treating symptomatic patients with toxin-positive stools, but some spores may survive, and relapse is frequent. Metronidazole is the *drug of choice* since oral treatment with vancomycin can select for vancomycin-resistant enterococci. Although diarrhea and pseudomembranous colitis can be caused by most antibacterial agents, the incidence in relation to the amount used appears to be highest for clindamycin. Allergic reactions (such as rashes and fever), hepatotoxicity, and neutropenia are observed only rarely.

## CHLORAMPHENICOL

Chloramphenicol causes two types of bone marrow suppression: a dose-related, reversible suppression of all elements, which occurs commonly during therapy at the maximal recommended doses (4 g/d in adults), and an idiosyncratic, irreversible aplastic anemia, which occurs in approximately 1 in every 25,000 to 40,000 exposures. The irreversible form has been reported to follow all types of chloramphenicol treatment, including ocular administration, and often develops months after therapy is discontinued.

In premature neonates and infants, chloramphenicol can cause a dose-related "gray syndrome" that is characterized by cyanosis, hypotension, and death and that results from an inability of the newborn to metabolize the drug. These potentially serious toxicities and the availability of newer drugs have substantially reduced the indications for chloramphenicol.

## TETRACYCLINES

Gastrointestinal effects are the most common adverse reactions to the tetracyclines. These problems may be related to a direct irritant effect, since tetracyclines can also cause esophageal ulceration when they dissolve before reaching the stomach. It is important that nighttime doses be taken with sufficient fluid. Concurrent food intake may improve tolerance, but absorption of tetracycline HCl is impaired when the drug is taken with food.

Hepatotoxicity has been reported after administration of >2 g of tetracycline intravenously and at lower doses during pregnancy. There are currently no indications for intravenous tetracycline treatment in pregnancy. All tetracyclines can cause phototoxic skin reactions; these reactions are most common with doxycycline. Other dermal reactions, including rash, are uncommon. Tetracyclines are contraindicated in children <8 years of age because of mottling of the permanent teeth; doxycycline may

be less likely than the other tetracyclines to cause this problem. Worsening of renal function in patients with preexisting renal dysfunction has been reported with use of tetracycline, although some of the increased azotemia may be due to amino acid catabolism. Doxycycline and perhaps minocycline appear to be free from these renal side effects. Alternative effective agents are nearly always available for use in patients with renal dysfunction. Minocycline can cause vertigo in up to 70% of women receiving therapeutic doses and in a lower percentage of men.

## SULFONAMIDES AND TRIMETHOPRIM

The sulfonamides are generally safe, but the list of possible adverse reactions is very long. These compounds occasionally cause a number of allergic reactions, from relatively minor skin rashes (including maculopapular rashes and urticarial reactions typically appearing after a week of therapy) to severe or even life-threatening reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The severe hypersensitivity reactions have occurred most commonly after treatment with the long-acting sulfonamides, such as sulfamethoxypyridazine, which are no longer used. Pyrimethamine plus sulfadoxine (Fansidar), used for malaria prophylaxis, may cause severe allergic reactions, including hepatic and hematologic toxicities, in addition to dermatologic toxicity. Photosensitivity reactions are also relatively common with sulfonamides.

Many patients infected with HIV who receive trimethoprim-sulfamethoxazole have adverse dermatologic reactions. These reactions are usually not life-threatening and appear to regress in many cases despite continuation of therapy. In high doses, trimethoprim interferes with the renal secretion of potassium. Hyperkalemia is relatively common among HIV-positive patients and is most often found after 7 days of trimethoprim-sulfamethoxazole therapy for pneumonia caused by *Pneumocystis carinii*.

Sulfonamides and trimethoprim may also cause severe hematologic complications, including agranulocytosis, hemolytic and megaloblastic anemia, and thrombocytopenia. These dose-related side effects may be greater in patients with renal insufficiency. Hemolytic anemia is most common in patients with glucose-6-phosphate dehydrogenase deficiency who take long-acting compounds; trimethoprim-sulfamethoxazole rarely causes hemolysis in such subjects. Granulocytopenia from trimethoprim-sulfamethoxazole is especially common in HIV-infected patients, occurring in 10 to 50% of this group.

Renal insufficiency, caused by crystals of the relatively insoluble acetyl metabolite, is observed primarily with the long-acting sulfonamides. Many cases of crystalluria in HIV-infected patients taking sulfadiazine for toxoplasmosis have been reported. A high level of fluid intake may prevent this complication.

It is recommended that sulfonamides not be administered to the newborn because of concerns that bilirubin may be displaced from protein-binding sites, with subsequent jaundice and kernicterus.

In addition to the preceding problems, sulfonamides may occasionally cause drug fever with serum sickness, hepatic toxicity (including necrosis), and systemic lupus

erythematosus.

## FLUOROQUINOLONES

Fluoroquinolones are relatively safe; adverse reactions rarely require discontinuation of therapy. The most common reactions include gastrointestinal distress, such as nausea or diarrhea (<5%), and central nervous system effects, including insomnia and dizziness (<5%). Trovafloxacin is prone to causing dizziness, especially among women. However, of more serious concern is the report of more than 100 cases of symptomatic liver toxicity in patients receiving trovafloxacin, including 14 cases of acute liver failure strongly associated with trovafloxacin exposure. As a result, the Food and Drug Administration has recommended that this quinolone be used only in hospitalized patients with serious or life-threatening conditions in which the benefits offered by the drug outweigh its potential risks. Phototoxicity can be severe, especially with sparfloxacin. Rarely, hepatic and renal dysfunction and anaphylactoid and allergic reactions are observed. Tendon rupture has also been associated with quinolone use in rare instances. The use of these drugs is contraindicated in patients <18 years of age because of evidence in animals of cartilage damage in developing joints. In carefully selected situations in which the perceived benefits outweigh the risks (e.g., in adolescent patients with cystic fibrosis who have pulmonary exacerbations), fluoroquinolones may be useful for short-term therapy. They are contraindicated in pregnancy because of concern for the developing fetus.

## RIFAMPIN

Rifampin is generally well tolerated but has several important side effects. Some patients have transient rises in hepatic aminotransferases, but these levels usually return to normal without discontinuation of the drug. Although hepatitis from rifampin itself develops only rarely, the drug is thought by some investigators to potentiate the hepatic toxicity of concomitantly administered isoniazid. Intermittent administration of rifampin (usually fewer than three times per week) has been associated with symptoms that seem to have an immunologic basis. These include flulike symptoms and (rarely) hemolysis, thrombocytopenia, shock, and renal failure. Minor gastrointestinal side effects, skin rashes, and interstitial nephritis have also been reported. Patients should be warned that rifampin and its metabolites cause secretions such as urine, tears, sweat, and saliva to turn orange and that contact lenses may be stained.

## METRONIDAZOLE

Serious adverse reactions to metronidazole are uncommon. Gastrointestinal side effects such as nausea are most frequent but rarely necessitate discontinuation of therapy. Pseudomembranous colitis in association with metronidazole has been reported but is very rare. A metallic taste is relatively common, and stomatitis and glossitis are occasionally reported. Disulfiram-like reactions can occur if ethanol is ingested concurrently. Peripheral neuropathy develops in some patients, and seizures and encephalopathy have been reported after high doses and in patients with hepatic failure.

Concerns about mutagenicity and carcinogenicity from metronidazole have led to recommendations that it not be used in pregnancy (especially during the first trimester)

when alternative agents are available. Although retrospective studies have found no association between metronidazole and carcinogenesis, long-term administration of high doses should be avoided when therapeutic alternatives exist.

## DRUG INTERACTIONS

Historically, clinically important interactions involving antibacterial drugs were generally of little concern, since b-lactams were the most widely used agents and rarely interacted with other drugs in a manner that affected the patient adversely. However, fluoroquinolones, macrolides, and rifampin are now more widely used, and interactions are of increasing concern.Table 137-3 lists the most common and best-documented interactions of antibacterial agents with other drugs and characterizes the clinical relevance of these interactions. Coadministration of drugs paired inTable 137-3 does not necessarily have clinically important adverse consequences. The result depends on the timing of administration, the dose and duration of therapy, the baseline serum concentration of the non-antibacterial drug administered, the patient's susceptibility to the pharmacologic effect of the non-antibacterial drug, and other, less-well-described cofactors. Recognition of the potential for an interaction before the administration of an antibacterial agent is crucial to the rational use of these drugs, since adverse consequences can often be prevented if the interaction is anticipated.Table 137-3 is intended only to heighten awareness of the potential for an interaction. Additional sources should be consulted to identify appropriate options.**For further discussion of drug interactions, see Chap. 70.*

### MACROLIDES

Erythromycin and clarithromycin can inhibit the P450 enzyme CYP3A and thus the metabolism of many concurrently administered drugs, such as cisapride, theophylline, carbamazepine, terfenadine, astemizole, warfarin, and ergot alkaloids. The magnitude of the theophylline interaction is highly variable and is proportional to the dose and duration of erythromycin treatment. In contrast, cyclosporine levels predictably increase when erythromycin is administered, since CYP3A is responsible for cyclosporine metabolism. Decreased metabolism of terfenadine, astemizole, cisapride, and pimozide has been reported to cause severe cardiac dysfunction. Azithromycin has little effect on the metabolism of other drugs. In approximately 10% of patients receiving digoxin, concentrations increase when erythromycin is also given.

### TETRACYCLINES

The most important interaction involving tetracyclines is the reduction in absorption when these drugs are coadministered with di- and trivalent cations, such as antacids, iron compounds, or dairy products. A similar interaction is seen with quinolones (see below). Food also adversely affects absorption of most tetracyclines. Inducers of hepatic isoenzymes, such as phenytoin and barbiturates, increase the clearance of doxycycline; although the clinical significance of this effect is unknown, use of an alternative antibiotic may be appropriate.

### SULFONAMIDES

Sulfonamides may increase the hypoprothrombinemic effect of warfarin by inhibition of its metabolism and possibly by protein-binding displacement. Sulfonamides may also potentiate the effects of oral hypoglycemic agents and phenytoin through reduction in metabolism or displacement from serum protein.

### FLUOROQUINOLONES

There are two clinically important drug interactions involving fluoroquinolones. First, like tetracyclines, all fluoroquinolones are chelated by divalent and trivalent cations, which prevent most of the dose from being absorbed. Second, certain fluoroquinolones (grepafloxacin, ciprofloxacin, and -- to a much lesser extent -- levofloxacin and trovafloxacin) can inhibit hepatic enzymes that metabolize theophylline, with resultant theophylline toxicity. The same mechanism accounts for increases in serum caffeine concentrations, but the clinical significance of this interaction is unknown. Scattered reports indicate that quinolones can also potentiate the nephrotoxicity of cyclosporine, exaggerate the effects of warfarin, and increase neurotoxicity when coadministered with nonsteroidal anti-inflammatory agents. However, these interactions have not been confirmed by controlled trials.

### RIFAMPIN

Rifampin is an excellent inducer of many cytochrome P450 enzymes and increases the hepatic clearance of a number of drugs, including the following (with the indicated predictable outcomes): HIV-1 protease inhibitors (loss of viral suppression), oral contraceptives (pregnancy), warfarin (decreased prothrombin times), cyclosporine and prednisone (organ rejection or exacerbations of any underlying inflammatory condition), and verapamil and diltiazem (increased dosage requirements). Before rifampin is prescribed for any patient, a review of concomitant drug therapy is essential.

### METRONIDAZOLE

Metronidazole can cause a disulfiram-like syndrome when alcohol is ingested; thus, patients taking metronidazole should be instructed to avoid alcohol. Inhibition of the metabolism of warfarin by metronidazole leads to significant rises in prothrombin times.

## PROPHYLAXIS OF BACTERIAL INFECTIONS

Antibacterial agents are occasionally indicated for use in patients who have no evidence of infection but who have been or are expected to be exposed to bacterial pathogens under circumstances that constitute a major risk of infection. The basic tenets of antimicrobial prophylaxis are as follows: First, the risk or potential severity of infection should be greater than the risk of side effects from the antibacterial agent. Second, the antibacterial agent should be given for the shortest period necessary to prevent target infections. Third, the antibacterial agent should be given before the expected period of risk (e.g., surgical prophylaxis) or as soon as possible after contact with an infected individual (e.g., prophylaxis for meningococcal meningitis).

Table 137-4 lists the major indications for antibacterial prophylaxis in adults. (The use of antibacterial agents in children to prevent rheumatic fever and otitis media under certain

circumstances is also common practice.) The table includes only those indications that are widely accepted, supported by well-designed studies, or recommended by expert panels. Prophylaxis is also used but is less widely accepted for recurrent cellulitis in conjunction with lymphedema, recurrent pneumococcal meningitis in conjunction with deficiencies in humoral immunity orCSFleaks, traveler's diarrhea, gram-negative sepsis in conjunction with neutropenia, and spontaneous bacterial peritonitis in conjunction with ascites.

The major use of antibacterial prophylaxis in the United States is for infections following surgical procedures. Antibacterial agents are administered just before the surgical procedure -- and, for long operations, during the procedure as well -- to ensure high levels in serum and tissues during surgery. The objective is to eradicate bacteria originating from the air of the operating suite, the skin of the surgical team, or the patient's own flora that may contaminate the wound. In all but colorectal surgical procedures, prophylaxis is predominantly directed against staphylococci. Prophylaxis is intended to prevent wound infection or infection of implanted devices, not all infections that may occur during the postoperative period (e.g., urinary tract infections or pneumonia). Prolonged prophylaxis merely alters the normal flora and favors infections with organisms resistant to the antibacterial agents used.

## ANTIBACTERIAL COSTS AND INAPPROPRIATE USE

Use of antibacterial agents in hospitals in the United States accounts for an important percentage of all drug costs and may represent the largest expenditure for any pharmacologic class. In the outpatient setting, the costs of antibacterial drugs are second only to those of cardiovascular agents. A survey of office-based physicians found that between 1980 and 1992 there was a marked increase in the use of expensive broad-spectrum antimicrobials. It is not unusual for the purchase cost (in 2000 dollars) of a newer parenteral antibiotic to be $1000 to $2000 for a 10- to 14-day course of treatment. Therapy with a new oral antibiotic can easily cost $50 to $75. Administration costs, monitoring costs, and pharmacy charges must be added to these figures. While some newer antibacterial agents undeniably represent important advances in therapy, many newer drugs offer no advantage over older, less expensive agents.

Clinicians are understandably confused by the bewildering array of available drugs. Numerous surveys have reported that approximately 50% of antibiotic use is in some way "inappropriate." Aside from the monetary cost of unnecessary antibiotics, there are the costs of excess morbidity from adverse effects and drug interactions and the eventual costs of treating more resistant organisms. The following suggestions are intended to provide guidance through the antibiotic maze.

First, objective evidence regarding the merits of newer drugs is available through publications such as *The Medical Letter*, including the annual update of *Drugs of Choice*. Second, clinicians should become comfortable using a few drugs recommended by independent experts and should resist the temptation to use a new drug unless the merits are clear. A new antibacterial agent with a "broader spectrum and greater potency" or a "longer half-life and higher tissue levels" does not necessarily mean greater clinical efficacy. Third, the clinician must become familiar with local bacterial

susceptibility profiles. It may not be necessary to use a new drug with "improved activity against *P. aeruginosa*" if that pathogen is rarely encountered or if it retains full susceptibility to older drugs. Finally, with regard to inpatient use of antibacterial drugs, appropriate empirical treatment with one or more broad-spectrum agents may often be simplified, with use of a narrower-spectrum agent or even an oral drug, once the results of cultures and susceptibility tests become available. While there is an understandable temptation not to alter effective therapy, switching to a more specific agent, once the patient has improved clinically, does not compromise eventual outcome. If these guidelines are followed, the care of patients will not be undermined, many unnecessary complications and expenses will be avoided, and the useful life of valuable drugs will be extended.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 5 -DISEASES CAUSED BY GRAM-POSITIVE BACTERIA

## 138. PNEUMOCOCCAL INFECTIONS - *Daniel M. Musher*

*Streptococcus pneumoniae* (the pneumococcus) was recognized as a major cause of pneumonia in the 1880s and has been a central focus of study leading to the modern understanding of humoral immunity. The name *Diplococcus pneumoniae* was assigned to the organism in 1926 on the basis of its appearance in Gram-stained sputum. In 1974, the organism was renamed *Streptococcus pneumoniae* because of its growth in chains in liquid medium. Around 1900, pneumococcal serotypes were recognized when the injection of killed organisms into a rabbit stimulated the production of serum antibody that agglutinated and caused increased capsular density of the immunizing strain as well as of some but not all other pneumococcal isolates. Ninety serotypes have now been identified, each possessing a unique polysaccharide capsule.

### MICROBIOLOGY

Pneumococci are identified in the clinical laboratory as gram-positive cocci that grow in chains and are catalase-negative. They produce pneumolysin, a toxin that breaks down hemoglobin into a greenish degeneration product, thereby causinga hemolysis on blood agar. More than 98% of pneumococcal isolates are susceptible to ethylhydrocupreine (optochin), and virtually all pneumococcal colonies are dissolved by bile salts.

Peptidoglycan and teichoic acid are the principal constituents of the pneumococcal cell wall. The cell wall's integrity depends on the presence of numerous peptide side chains cross-linked by the activity of enzymes such as trans- and carboxypeptidases.b-Lactam antibiotics inactivate these enzymes by covalently binding their active site. Unique to *S. pneumoniae* and present in all strains is C (for "cell-wall") substance, a polysaccharide consisting of teichoic acid with a phosphorylcholine residue. Surface-exposed choline-binding proteins serve as a site of attachment for potential virulence factors, such as PspA, which may prevent phagocytosis. Nearly every clinical isolate of *S. pneumoniae* has a polysaccharide capsule.

There are two systems for numbering the 90 known distinct capsules of *S. pneumoniae*. In the American system, serotypes are numbered in the order in which they were identified. The strains that most frequently cause human disease were generally the earliest to be identified and thus tend to have lower numbers. The more widely accepted Danish system places serotypes into groups based on antigenic similarities; for example, Danish group 19 includes types 19F ("first recognized"), 19A, 19B, and 19C, which in the American system would be types 19, 57, 58, and 59, respectively. Serotyping was clinically relevant in the 1930s, when type-specific antisera were administered as therapy, and (although genetic typing is more specific) it has again become important for epidemiologic studies of the spread of antibiotic-resistant isolates in communities and among countries. Capsule switching has been documented and to some extent limits the epidemiologic reliability of serotyping.

### EPIDEMIOLOGY

*S. pneumoniae* colonizes the nasopharynx and can be isolated from 5 to 10% of healthy

adults and from 20 to 40% of healthy children. Once the organisms have colonized an adult, they are likely to persist for 2 to 4 weeks but may persist for as long as 6 months. Pneumococci spread from one individual to another as a result of extensive close contact; transmission may be enhanced by poor ventilation. Day-care centers have been a site of spread, especially of penicillin-resistant strains of serotypes 6B, 14, 19F, and 23F. Outbreaks occur among adults in crowded living conditions -- e.g., in military barracks, prisons, and shelters for the homeless -- as well as among susceptible populations in settings such as nursing homes. The risk of pneumococcal pneumonia is not increased by contact in schools or workplaces (including hospitals).

The incidence of pneumococcal bacteremia is relatively high among infants up to 2 years of age and low among teenagers and young adults; rates increase beginning at around age 55. A surveillance study in South Carolina showed the incidences of pneumococcal bacteremia among infants, young adults, and persons³70 years of age to be 160, 5, and 70 cases per 100,000 population, respectively. Most cases of pneumococcal bacteremia in adults are due to pneumonia, and there are three to four cases of nonbacteremic pneumonia for every bacteremic case. Thus, it is estimated that there are 20 cases of pneumococcal pneumonia annually per 100,000 young adults and 280 cases annually per 100,000 persons over the age of 70. The incidence of pneumococcal bacteremia among adults exhibits a distinct midwinter peak and a striking dip in summer. In children, the incidence of bacteremia is relatively constant throughout the year except for a marked dip in midsummer. For reasons that are unclear, certain populations, including Native Americans, Native Alaskans, and African Americans, appear to be unusually susceptible to invasive pneumococcal disease. This enhanced susceptibility, not unlike that to infection with *Haemophilus influenzae*, is thought to have a genetic basic that thus far remains unelucidated.

## PATHOGENETIC MECHANISMS

*S. pneumoniae* attaches to human nasopharyngeal cells through the specific interaction of bacterial surface adhesins, such as pneumococcal surface antigen A or choline-binding proteins, with epithelial cell receptors. Epithelial cell glycoconjugates containing the disaccharide GlcNAcb1-4Gal or asialo-GM1 glycolipid are possible binding sites. Pneumococcal phase variation, in which organisms switch between transparent and opaque, may also play a role in adherence. Upon culture, a mixed population of transparent and opaque pneumococcal colonies can be identified. Organisms from opaque colonies have relatively little peptidoglycan and relatively large capsules; those from transparent colonies have much more phosphorylcholine (which contributes to their capacity to adhere to mammalian cells) and less capsular polysaccharide. When an opaque colony is inoculated intranasally into an experimental animal, only those organisms that form transparent colonies persist. In contrast, after intraperitoneal inoculation, organisms that yield transparent colonies are rapidly cleared from the blood, while those that make opaque colonies resist clearance.

Once the nasopharynx has been colonized, infection results if the organisms are carried into anatomically contiguous areas such as the eustachian tubes or the nasal sinuses and if their clearance is hindered, for example, by mucosal edema due to allergy or viral infection. Similarly, pneumonia ensues if organisms are inhaled or aspirated into the bronchioles or alveoli and then are not cleared -- in many cases, because viral infection

or cigarette smoke or other toxic substances have increased mucus production and/or damaged ciliary action. A mechanism by which pneumococci may bind to pneumocytes after viral infection has been suggested. Pneumocytes activated by cytokines have been shown to express the receptor for platelet-activating factor. This receptor binds the phosphorylcholine residue on pneumococcal C substance, facilitating the adherence of pneumococci. Studies suggest that pneumococci may invade tissues by penetrating mucosal layers; the clinical significance of this finding remains to be determined.

Once pneumococci reach an area where they do not naturally belong, they activate complement by classic and alternative pathways and stimulate cytokine production, which leads to the attraction of polymorphonuclear neutrophils (PMNs). The polysaccharide capsule, however, renders the organisms resistant to phagocytosis. In the absence of anticapsular antibody, phagocytic cells such as alveolar macrophages have a limited capacity to ingest and kill pneumococci; a large bacterial inoculum and/or the compromise of phagocytic function allows the initiation of lung infection. Infection of the meninges, joint spaces, bones, and peritoneal cavity results from the spread of pneumococci through the bloodstream, usually but not always from a recognized focus of infection in the respiratory tract.

The capacity to cause disease reflects the ability of pneumococci to escape ingestion and killing by host phagocytic cells, on the one hand, and to stimulate an inflammatory response and damage tissues, on the other. Encapsulated pneumococci are poorly ingested and killed in vivo in the immunologically naive host or in vitro by mammalian phagocytic cells in the absence of anticapsular antibody and complement. Unencapsulated pneumococci virtually never cause invasive disease (although they can cause conjunctivitis), and mutants lacking a capsule are essentially avirulent in experimental animals. Symptoms of disease are largely attributable to the generation of an inflammatory response that may cause pain by increasing pressure (as in otitis media) or may interfere with vital bodily functions, such as oxygenation of blood (as in pneumonia) or cerebral function (as in meningitis). Cell-wall constituents of *S. pneumoniae*, including teichoic acid, C substance, and (in particular) peptidoglycan, activate complement by the alternative pathway; the reaction between cell-wall structures and antibody also activates the classic complement pathway. The result is the release of C5a, a potent attractant forPMNs, into the surrounding medium. Inflammation is also facilitated by the ability of peptidoglycan to stimulate cytokine production, which activates endothelial cells to express selectin and integrin receptors for inflammatory cells. Inflammation in the central nervous system (CNS) during meningitis is a major contributor to neuronal cell injury. Pneumolysin, a thiol-activated toxin, exerts a variety of effects on ciliary cells and PMNs and also activates the classic complement pathway by direct binding of Clq. Injection of pneumolysin into the lungs of experimental animals produces the histologic features of pneumonia; in mice, immunization with this substance or challenge with genetically engineered mutants that do not produce pneumolysin is associated with a significant reduction in virulence. Autolysin may contribute to the pathogenesis of pneumococcal disease by lysing bacteria, thereby releasing their constituents and heightening the reaction with human tissues. The release of excitatory amino acids in neuronal tissue may contribute to damage caused by meningitis.

**HOST DEFENSE MECHANISMS**

Mechanisms of host defense may be immunologically nonspecific or specific. Nonspecific mechanisms include laminar airflow across mucous layers that filter inspired air, the glottal reflex, laryngeal closure, the cough reflex, the clearance of organisms from the lower airways by ciliated cells, and the ingestion by pulmonary macrophages andPMNs of small bacterial inocula that manage to reach alveolar spaces. Respiratory virus infection, chronic pulmonary disease, or heart failure compromises these mechanisms, predisposing to the development of pneumococcal pneumonia. Antibody to PspA and other pneumococcal constituents such as pneumolysin may be prevalent in the population and may contribute to immunity that is immunologically specific but not type specific.

Anticapsular antibody provides serotype-specific protection against pneumococcal infection. However, most healthy adults lack IgG antibody to most pneumococcal capsular polysaccharides. Antibody appears after colonization, infection, or vaccination. In the first few weeks after colonization, nonspecific mechanisms probably protect the host from infection. Thereafter, newly developed anticapsular antibody provides a high degree of specific protection. In contrast to this normal situation, adults who are at risk of aspirating pharyngeal contents and/or who have diminished mechanisms of lower airway clearance are at risk of developing pneumonia before antibody is produced. Similarly, children whose nasal mucosal membranes become acutely congested around the time of colonization are at risk of developing otitis media. Persons with a diminished capacity to form antibody remain susceptible for as long as they are colonized.

The risk of serious pneumococcal infection is greatly increased in persons with conditions that compromise IgG synthesis and/or the phagocytic function ofPMNs and macrophages; this risk is also elevated in the presence of conditions associated with debilitation or malnutrition. Nearly all adults who are hospitalized for pneumococcal pneumonia have at least one of the conditions listed inTable 138-1 and/or fall into one of the groups known to be at high risk on epidemiologic grounds. Prior hospitalization either predisposes to or serves as a strong marker for pneumococcal infection. The susceptibility of elderly individuals to pneumococcal pneumonia may reflect diminished clearance mechanisms as well as debilitation, malnutrition, and comorbid diseases. Although IgG responses to capsular polysaccharides, as measured by enzyme-linked immunosorbent assay (ELISA), are more or less normal in elderly persons, the functional capacity of the antibody appears to be decreased. The remarkably high incidence of pneumococcal infection -- perhaps 100-fold above baseline -- among persons with AIDS is noteworthy.

Once a pneumococcal infection has been initiated, the absence of a spleen predisposes to fulminant disease. The liver is able to remove opsonized (antibody-coated) pneumococci from the circulation; in the absence of antibody, however, only the slow passage of blood through the splenic sinuses and prolonged contact with reticuloendothelial cells in the cords of Billroth allow time for bacterial clearance. Patients without spleens may die of pneumococcal pneumonia and sepsis at such an early stage of the illness that pulmonary consolidation is not evident on x-ray before death but rather is found only at autopsy.

## SPECIFIC INFECTIONS CAUSED BY *S. PNEUMONIAE*

*S. pneumoniae* causes infections of the middle ear, sinuses, trachea, bronchi, and lungs (Table 138-2) by direct spread from the nasopharyngeal site of colonization. Infections of theCNS, heart valves, bones, joints, and peritoneal cavity usually arise by hematogenous spread; in rare cases peritoneal infection develops via ascent through the fallopian tubes. The CNS may also be infected by contiguous spread of organisms, as in patients who have a tear in the dura. Primary bacteremia -- i.e., the presence of pneumococci in the blood with no apparent source -- occurs commonly in children under 2 years of age and as a small percentage of all pneumococcal bacteremias in adults; if no therapy is given, a source may become apparent. Pleural infection results either from direct extension of pneumonia to the visceral pleura or from hematogenous spread of bacteria from a pulmonary or extrapulmonary focus; the route cannot be determined in any individual case.

**Otitis Media and Sinusitis** When fluid from the middle ear is cultured during acute otitis media or fluid from a paranasal sinus is cultured during acute sinusitis, *S. pneumoniae* is the most common isolate or is second only to nontypable *H. influenzae*. Whether in adults or in children, pneumococci are identified in about 40 to 50% of cases of otitis in which an etiologic agent is isolated. Prior infection by a respiratory virus or allergy is thought to contribute significantly to these pneumococcal infections by causing congestion of the openings to the eustachian tubes or the paranasal sinuses. Prospective studies of young children have shown that colonization precedes infection in most cases. For reasons that are unclear, serotypes 6B, 14, 19F, and 23F predominate both as colonizing and as infecting organisms of children; therefore, these serotypes are currently being studied most intensively for use in vaccines to be administered to young children.

**Meningitis** Except during outbreaks of meningococcal infection, *S. pneumoniae* is the most common etiologic agent of bacterial meningitis in adults. Because of the remarkable success of *H. influenzae* type b vaccine, *S. pneumoniae* now predominates among cases in infants and toddlers as well (but not among those in newborns). Meningitis develops either by the direct extension of infection from the sinuses or the middle ear or as a result of bacteremia with seeding of the choroid plexus. Favoring the former possibility are the association between acute otitis media and meningitis as well as the documented role of *S. pneumoniae* as the most common cause of recurrent bacterial meningitis associated with head trauma, cerebrospinal fluid (CSF) leak, and/or dural tear. Favoring the latter are the association between pneumococcal bacteremia from any source and meningitis as well as an autopsy study of temporal bone from children who died of bacterial meningitis, which yielded no evidence of extension from the middle ear.

In the meninges and subarachnoid space, pneumococcal peptidoglycan stimulates an intense inflammatory response mediated by the release of interleukin (IL)1, IL-6, C5a, tumor necrosis factor (TNF), and other proinflammatory cytokines. This inflammatory response results in raised intracranial pressure, brain edema, and decreased blood flow leading to meningismus, drowsiness, or coma. Focal neurologic signs may result from vasculitis with venous or arterial thrombosis, from cranial neuropathy due to entrapment or infarction, from local cerebritis, from subdural effusion, or from brain herniation (Chap. 372).

No distinctive clinical or laboratory feature differentiates meningitis due to *S. pneumoniae* from that due to other bacteria. Patients note the sudden onset of fever, headache, and stiffness or pain in the neck. Without treatment, there is a progression over 24 to 48 h to confusion and then obtundation. On physical examination, the patient looks acutely ill and has a rigid neck. In such cases lumbar puncture should not be delayed for computed tomography (CT) of the head unless papilledema or focal neurologic signs are evident. TypicalCSFfindings consist of pleocytosis (500 to 10,000 cells/uL) with a predominance ofPMNs, an elevated protein level (100 to 500 mg/dL), and a decrease in glucose content. If antibiotics have not been given, large numbers of pneumococci can be seen in a Gram-stained specimen of CSF in nearly all cases, and specific therapy can be administered, although *Listeria* may be misidentified as the pneumococcus. If an effective antibiotic has already been given, the number of bacteria may be greatly decreased and microscopic examination of a Gram-stained specimen may yield negative results. In this situation, immunologic methods for the detection of pneumococcal capsule in the CSF may identify an etiologic agent in up to two-thirds of cases, although these methods have fallen out of favor. Most physicians prefer to use empirical broad-spectrum antibiotic therapy until the etiologic agent has been definitively identified and its susceptibility has been reported.

**Pneumonia** The distinctive symptoms and signs of pneumococcal pneumonia are (1) cough and sputum production, which reflect the proliferation of bacteria and the resulting inflammatory response in the alveoli; (2) fever; and (3) radiographic detection of an infiltrate.

*Predisposing Conditions* Pneumococcal pneumonia is most common at the extremes of age. Despite the undisputed role of *S. pneumoniae* as a major pathogenic bacterium for humans, the great majority of adults with pneumococcal pneumonia have underlying diseases that predispose them to infection. Otherwise-healthy military recruits involved in outbreaks of infection may be an exception to this rule; however, many of those affected have an antecedent viral-type illness that may reduce normal host resistance. In addition to prior viral respiratory illness, the most common predisposing conditions are alcoholism, malnutrition, chronic pulmonary disease of any kind, cigarette smoking, infection with HIV, diabetes mellitus, cirrhosis of the liver, anemia, prior hospitalization for any reason, renal insufficiency, and coronary artery disease (with or without recognized congestive heart failure). HIV infection is such an important predisposing factor that some authorities recommend that any young adult with pneumococcal pneumonia be tested for antibody to HIV.

*Presenting Symptoms* Patients often present with a preexisting respiratory condition that has distinctly deteriorated. If a viral upper respiratory illness is the predisposing factor, the patient may have felt unwell for several days, with coryza or a nonproductive cough and low-grade fever; at the time of onset of pneumonia, the temperature may rise to 38.9 to 39.4°C (102 to 103°F), and sputum production becomes prominent. In a patient who has chronic bronchitis, the sputum may increase in volume, become yellow or green and thicker than usual, and be associated with a fever that becomes progressively higher over 48 to 72 h. In a small proportion of cases, the onset of disease follows a hyperacute pattern in which the patient suddenly has a single episode of shaking chills followed by sustained fever and a cough productive of blood-tinged

sputum. This clinical picture is unfortunately called "classic," a vague term that is best avoided because many physicians believe that it means "most common," which is clearly not the case. In elderly subjects, the onset of disease may be especially insidious and may not suggest pneumonia at all. Persons in their eighties may have minimal cough, no sputum production, and no fever, instead appearing tired or confused. For the reasons noted above, the most abrupt progression of pneumococcal disease is seen in patients who have previously undergone splenectomy; these individuals may go from apparent good health to death in as little as 24 h. In pneumonia, pleuritic chest pain may result from extension of the inflammatory process to the visceral pleura; persistence of this pain, especially after the first day or two of treatment, raises concern about empyema (see "Complications," below). Nausea and vomiting or diarrhea, sometimes quite prominent, occur in up to 20% of cases. Clearly, the range of symptoms is sufficiently broad that there is no characteristic presentation to distinguish pneumococcal from other types of bacterial pneumonia (or from some types of nonbacterial pneumonia).

*Physical Findings* Patients with pneumococcal pneumonia usually appear ill and have a grayish, anxious appearance that differs from that of persons with viral or mycoplasmal pneumonia. Typically, the temperature is 38.9 to 39.4°C (102 to 103°F), the pulse 90 to 110 beats per minute, and the respiratory rate >20 breaths per minute. Elderly patients may have only a slight temperature elevation or be afebrile. Hypothermia is associated with increased morbidity and mortality. Herpes labialis appears in a small percentage of cases. Pain may cause diminished respiratory excursion (splinting) on the affected side. Dullness to percussion is noted in about half of cases, and vocal fremitus is increased. Breath sounds may be bronchial or tubular, and crackles are heard in most cases if enough air is being moved to generate them. Flatness to percussion at the lung base and inability to detect the expected degree of diaphragmatic motion suggest the presence of pleural fluid, which raises the possibility of empyema; the failure to assess fremitus, to distinguish dullness from flatness by percussion, or to examine for diaphragmatic excursion may leave the physician at the mercy of often ambiguous radiologic interpretations. The finding of a heart murmur, certainly if new, raises concern about endocarditis, a rare but serious complication. Hypoxia or the generalized response to pneumonia may cause the patient to be confused, but the appearance of confusion should raise concern about meningitis. Obtundation or neck stiffness should lead to an immediate consideration of this complication.

*Radiographic Findings (Fig. 138-CD1)* Pneumococcal pneumonia involves only one lung segment or a portion thereof in one-fourth of cases; it involves more than one segment but only one lobe or a portion thereof in another one-fourth of instances. Thus multilobar disease is seen in half of cases. Air-space consolidation is the predominant finding and is detected in 80% of cases. Air bronchogram (visualization of the air-filled bronchus against a background of consolidation in the alveoli) is evident in fewer than half of cases and is more common in bacteremic than in nonbacteremic disease. In rare instances, pneumococcal pneumonia leads to a lung abscess; a malignancy or a mixture of anaerobic and microaerophilic organisms is likely to be implicated as well. Although some pleural fluid may actually be present in half of cases, no more than 20% of patients have a sufficient volume of fluid to allow aspiration, and in only a minority of these patients is empyema documented.

*General Laboratory Findings* The peripheral-blood white blood cell (WBC) count exceeds 12,000/uL in the great majority of patients with pneumococcal pneumonia. However, the count is<6000/uL in 5 to 10% of persons hospitalized for pneumococcal pneumonia. Such a low count is strongly associated with lethal disease and is often but not always associated with bone marrow suppression due to alcohol ingestion. The serum bilirubin level may be modestly elevated; hypoxia, inflammatory changes in the liver, and breakdown of red blood cells in the lung are all thought to contribute to this increase. Levels of lactate dehydrogenase may be elevated. A variety of other abnormalities may be present, reflecting the contributory role of underlying diseases.**Abnormalities of pleural fluid in empyema are reviewed in Chap. 255.*

*Differential Diagnosis* Patients who present with community-acquired pneumonia may actually have infection of the lungs due to one of many organisms. The extensive list includes the following: *H. influenzae* or *Moraxella catarrhalis* in persons with little to predispose them other than chronic or acute inflammation of the airways; *Staphylococcus aureus* in persons who take glucocorticoids or who have major anatomic disruption of the airways; *Streptococcus pyogenes*; *Neisseria meningitidis*; anaerobic species in persons who have seizures or may have aspirated oropharyngeal or gastric secretions for some other reason; *Legionella*; *Pasteurella multocida* in dog or cat owners; gram-negative bacilli, especially in persons with severely damaged lungs who are taking glucocorticoids; viruses, especially influenza virus (in season), adenovirus, or respiratory syncytial virus; *Mycobacterium tuberculosis*; fungi, including *Pneumocystis carinii* (depending upon epidemiologic factors and the possible presence of HIV infection); *Mycoplasma*; *Chlamydia pneumoniae*, especially in older adults; and *Chlamydia psittaci* in bird owners. Many older men with lung cancer present with pneumonia, as do persons who have acute-onset inflammatory pulmonary conditions of uncertain etiology or those with pulmonary embolus and infarction. The breadth of this list vividly illustrates the difficulty of using empirical therapy for community-acquired pneumonia. Many of these diseases require evaluation, and specific therapy is available for an increasing number. Moreover, pneumococci -- perhaps the most common cause of community-acquired pneumonia -- are increasingly resistant to available antibiotics. Taken together, these factors favor precise determination of the etiology of a pneumonia syndrome whenever possible.

*Diagnostic Microbiology* An etiologic role for the pneumococcus in pneumonia is strongly suggested by the microscopic demonstration of large numbers ofPMNs and slightly elongated gram-positive cocci in pairs and chains in the sputum (Plate VI-2). Capsules may be seen surrounding the bacterial forms. Examined areas of the slide must be free of buccal epithelial cells, which indicate the admixture of saliva with sputum; saliva may contain $10^7$viridans streptococci per milliliter. When characteristic microscopic findings are noted, the identification of *S. pneumoniae* in sputum culture strongly indicates pneumococcal infection of the lower respiratory tract. In the absence of such microscopic findings, the identification of pneumococci by culture may be nonspecific, reflecting colonization of the upper airways. Culture is also less sensitive than microscopic examination for identifying pneumococci. Since most pneumococci do not produce distinctively mucoid colonies, their identification in the laboratory depends on the ability to select putative pneumococcal colonies for further study from amonga-hemolytic streptococci of the mouth. In short, laboratory diagnosis by sputum culture relies on the quality of the specimen provided, the care with which the relevant

purulent component is separated for culture, and the assiduity with which a-hemolytic colonies are studied. These factors need to be considered when sputum cultures from patients who appear to have pneumococcal pneumonia are said to yield only "normal mouth flora" and when the medical literature describes what appear to be poor results of sputum culture. Because of the central role of microscopic examination in diagnosis, physicians may wish to view the slides with the microbiologist. Blood cultures yield *S. pneumoniae* in about 25% of cases of pneumococcal pneumonia. Modern, automated systems often yield positive blood cultures within 12 h after the sample is obtained.

*Complications* Empyema is the most common complication of pneumococcal pneumonia, occurring in about 2% of cases. As noted above, some fluid appears in the pleural space in a substantial proportion of cases of pneumococcal pneumonia, but this parapneumonic effusion usually reflects an inflammatory response to infection that has been contained within the lung, and its presence is self-limited. When bacteria reach the pleural space -- either hematogenously or as a result of contiguous spread, possibly across lymphatics of the visceral pleura -- empyema results. The finding of frank pus, a positive result on Gram's staining, or the presence of fluid with a pH of£7.1 indicates the need for aggressive and complete drainage, preferably by prompt insertion of a chest tube, with verification byCT that fluid has been removed. If there is no response, thoracotomy is indicated. Persistence of fever (even if low-grade) and leukocytosis after 4 or 5 days of appropriate antibiotic treatment for pneumococcal pneumonia suggests empyema. In this setting, the diagnosis is exceedingly likely if the x-ray shows the persistence of pleural fluid. At this stage, thoracotomy is often needed for cure. Aggressive drainage is likely to reduce morbidity and mortality from empyema (Chap. 262).

**Other Syndromes** The appearance of pneumococcal infection at other, usually sterile body sites indicates hematogenous spread, either during frank pneumonia or, in a smaller proportion of cases, from an inapparent focus of infection. A case of pneumococcal endocarditis is seen every few years at large tertiary-care hospitals. Purulent pericarditis due to this organism, occurring as a separate entity or together with endocarditis, is even rarer. Most cases of spontaneous bacterial peritonitis in children and some cases in adults are caused by *S. pneumoniae*. Peritonitis in women may be related to the use of an intrauterine contraceptive device, and pneumococcal infections of the female reproductive organs continue to be described. Septic arthritis can arise spontaneously in a natural or prosthetic joint or as a complication of rheumatoid arthritis. Osteomyelitis in adults tends to involve vertebral bones. Epidural and brain abscesses are rarely described. Cellulitis can develop and does so most often in persons who have connective tissue diseases or HIV infection. The appearance of any of these unusual pneumococcal infections in a young adult may suggest that tests for HIV infection should be undertaken.

## TREATMENT

**Antibiotic Susceptibility** b-Lactam antibiotics, the cornerstone of therapy for serious pneumococcal infection, bind covalently to the active site and thereby block the action of the cell-membrane enzymes (endo-, trans-, and carboxypeptidases) that are responsible for cell-wall synthesis. These enzymes were identified by their reaction with radiolabeled penicillin and thus are called *penicillin-binding proteins*. In the 1960s,

virtually all clinical isolates of *S. pneumoniae* were susceptible to penicillin (i.e., were inhibited in vitro by concentrations of<0.06 ug/mL). During the past 20 years in Europe and the past 10 years or so in the United States, a steadily increasing number of pneumococcal isolates have shown some degree of resistance to penicillin. Resistance results when spontaneous mutation or acquisition of new genetic material alters penicillin-binding proteins in a manner that reduces their affinity for penicillin, thereby necessitating a higher concentration of penicillin for their saturation. The genetic information acquired also conveys resistance to other antibiotics. Mutation and selection of strains in communities in the United States -- especially in areas of high antibiotic use, such as day-care centers -- and spread of identifiable strains from other countries where antibiotics are available without prescription have contributed to the prevalence of resistance.

For most of the antibiotic era, pneumococcal susceptibility was not studied in vitro because of the organism's high degree of susceptibility to virtually all recommended antibiotics. Clearly, the situation has changed, and it seems important to study pneumococcal isolates, especially those causing invasive disease, for antibiotic susceptibility. In 1997, about 20% of pneumococcal isolates in the United States were intermediately susceptible to penicillin [minimal inhibitory concentration (MIC), 0.1 to 1.0 ug/mL] and 15% were resistant (MIC,³ 2.0 ug/mL;Table 138-3). The clinical significance of the MIC varies with the infection being treated. An intermediately resistant strain (e.g., MIC = 0.5 ug/mL) behaves as a susceptible organism when it causes pneumonia, but probably not when it causes otitis and certainly not when it causes meningitis. As a result, susceptibility may eventually be redefined on the basis of the site infected -- a concept supported by pharmacokinetic considerations and validated by outcome studies. Amoxicillin, with two- and fourfold lower MICs, appears to be more active against *S. pneumoniae* than penicillin -- thus the emerging preference for amoxicillin. Penicillin-susceptible pneumococci are susceptible to all commonly used cephalosporins. Penicillin-intermediate strains are resistant to all first- and many second-generation cephalosporins (of which cefuroxime retains the best efficacy) but are susceptible to some third-generation cephalosporins, including cefotaxime, ceftriaxone, cefepime, and cefpodoxime. One-half of highly penicillin-resistant pneumococci are also resistant to cefotaxime and ceftriaxone, a higher proportion are resistant to cefepime, and nearly all are resistant to cefpodoxime. Pneumonia caused by intermediately penicillin-resistant strains responds well to b-lactam antibiotics. Pneumonia due to fully resistant strains also responds, but probably not as reliably; data that address this issue are currently being examined. Sinusitis and otitis media caused by intermediately resistant *S. pneumoniae* do not reliably respond to therapy, and failure of therapy may be common when these conditions are caused by highly resistant pneumococcal strains.

Resistance to erythromycin extends to the new macrolides, including azithromycin and clarithromycin. This resistance will certainly affect empirical therapy for bronchitis, sinusitis, and pneumonia. In the United States, the majority of macrolide-resistant pneumococci bear the so-called M phenotype (erythromycinMIC= 1 to 8 ug/mL) and are susceptible to clindamycin. In this case, resistance is mediated by an efflux pump mechanism; it is not yet known whether M-type resistance can be overcome by clinically achievable levels of macrolides. In Europe, most macrolide resistance is due to a mutation in *ermB*, which confers high-level resistance not only to macrolides but also to

clindamycin. Rates of resistance to doxycycline among pneumococci of varying susceptibility to penicillin are similar to those observed for macrolides, whereas the overall rate of pneumococcal resistance to trimethoprim-sulfamethoxazole (25%) is sufficiently high to discourage therapy with this agent unless an isolate is known to be susceptible.

The newer fluoroquinolones remain highly effective against pneumococci, with equal efficacy against penicillin-susceptible and -resistant strains. All pneumococci are susceptible to vancomycin, although it is feared that the acquisition of vancomycin resistance by enterococci and other gram-positive bacteria may eventually lead to pneumococcal transformation to resistance. Of drugs under study, the oxazolidinones and glycopeptides appear to be most promising, withMICs for drug-resistant *S. pneumoniae* strains no higher than for penicillin-susceptible strains. Resistance to streptogramins parallels that to macrolides and limits the usefulness of these drugs for the treatment of pneumonia.

*Pneumococcal susceptibility patterns vary greatly between and even within individual communities and the data are in a state of flux.* It does appear, however, that the constant trend is toward more widespread resistance.

**General Therapy** There has been increased emphasis on outpatient therapy in patients who are at low risk (as determined by PORT score according to criteria described by the Pneumonia Outcomes Research Team; Chap. 255). This approach appears to be safe. However, if the physician is in doubt about the severity of illness, the social circumstances, or the likelihood of compliance with the prescribed antibiotic regimen, it may be best to hospitalize the patient, at least briefly.

**Specific Antibiotic Therapy**

***Pneumonia*** This section will deal primarily with the treatment of pneumonia that is known to be due to *S. pneumoniae*. The broader issue of empirical therapy for community-acquired pneumonia is covered in detail elsewhere (Chap. 255). However, a few general comments on empirical therapy apply. An important problem in treating pneumonia is that, without a good sputum sample that can be Gram-stained and examined microscopically, the etiologic agent is not known at the time when treatment needs to be initiated and is not likely to become known later. Empirical therapy in such cases must be effective against *S. pneumoniae*, which remains the most likely causative agent of community-acquired pneumonia, unless epidemiologic, clinical, and radiologic findings strongly favor another etiologic entity. If a good sputum sample is obtained and only *S. pneumoniae* is visible, therapy can be focused on this organism, although additional treatment may be added for organisms that are not visualized microscopically -- e.g., influenza virus in a patient hospitalized during an influenza outbreak. Even if the pneumococcus is suspected, a certain degree of empiricism is required, because the antibiotic susceptibility of the strain involved will not be known for 1 or 2 days.

*OUTPATIENT THERAPY* Amoxicillin (500 mg four times daily) effectively treats all cases of pneumococcal pneumonia except those caused by the most highly penicillin-resistant isolates. Neither cefuroxime nor cefpodoxime offers any advantages

over amoxicillin since these drugs are less likely, even at high dosages, to be active against highly resistant pneumococcal strains. One of the newer fluoroquinolones in an accepted dosage for pneumonia is highly likely to be effective. Doxycycline, azithromycin, or clarithromycin will be effective in 85 to 90% of cases and clindamycin in a higher proportion. The trend toward increasing resistance to all these drugs is worrisome. Because one-fourth of all isolates are now resistant to trimethoprim-sulfamethoxazole, this agent can no longer be recommended. Since none of these therapies ensures the kind of antibiotic coverage that it would have in the past, patients should be instructed to remain in close contact with the prescribing physician, especially if there is any deterioration in their condition. It is worth noting that an outcomes study using data from the mid-1990s, when the rate of resistance was lower, showed that treatment with any of the above-mentioned antibiotics was associated with a good outcome; the majority of cases in which an etiologic agent was identified were due to *S. pneumoniae*.

*INPATIENT THERAPY* Pneumonia caused by penicillin-susceptible or intermediately penicillin-resistant pneumococcal isolates is readily treatable with penicillin. The dosages that follow are acceptable against intermediately resistant strains and against many or most fully resistant isolates, although they are excessive for use against susceptible isolates. Lower doses, however, cannot be recommended initially because susceptibility is not known until 24 to 72 h after treatment is begun. Patients who are sick enough to be hospitalized should be treated promptly. Most physicians favor parenteral antibiotics, although oral administration of well-absorbed drugs may be acceptable if the patient is not vomiting or hypotensive. Recommended regimens include ceftriaxone (1 to 2 g/d) or cefotaxime (1 to 2 g every 6 to 8 h). Ampicillin (1 to 2 g every 6 h) is also widely used. A quinolone or azithromycin can be given parenterally or orally. About 10 to 15% of all pneumococci are resistant to macrolides, and 1 to 2% are resistant to quinolones. Much of the resistance to macrolides among pneumococcal isolates may be overcome by the administration of azithromycin at a dosage of 500 mg on the first day and 250 mg/d thereafter. Clindamycin is effective against a higher proportion of resistant pneumococci than are the macrolides. Vancomycin is uniformly effective against pneumococci and should be used for initial therapy if there is reason to believe that a patient is infected with a strain that is resistant to the drugs listed above. As antimicrobial resistance among pneumococci evolves, updated recommendations will be issued by the Infectious Diseases Society of America, the American Thoracic Society, and the Centers for Disease Control and Prevention (CDC).

Patients with severe allergic reactions to b-lactam antibiotics should receive vancomycin (500 mg intravenously every 6 h) or a quinolone. As noted above, there have always been treatment failures unrelated to the antimicrobial susceptibility of the organism; nevertheless, the failure of a patient to respond promptly should raise the question of resistance, and vancomycin should be given until the susceptibility of the infecting strain to other drugs has been documented. Of course, evidence for loculated infections (such as empyema) and/or other causes of fever should be sought.

*DURATION OF THERAPY* The optimal duration of treatment for pneumococcal pneumonia is uncertain. Penicillin-susceptible strains disappear from the sputum within several hours of the first dose of penicillin, and a single dose of procaine penicillin, which results in the maintenance of an effective antimicrobial level for 24 h, was said to

cure pneumococcal pneumonia in otherwise-healthy young adults at the time when all isolates were susceptible. Most older physicians treat pneumococcal pneumonia for 5 to 10 days. In the absence of reports of therapy failure, younger physicians have tended to treat the infection for 10 to 14 days. Prolongation of therapy is a two-edged sword, especially in debilitated patients, because the risk of complications increases with each day of antibiotic treatment, particularly in the hospital setting. A few days of close observation and parenteral therapy followed by an oral antibiotic -- with the entire course of treatment continuing for no more than 5 days after the patient becomes afebrile -- may be the best approach.

***Otitis Media and Acute Sinusitis*** Current treatment recommendations for otitis media and acute sinusitis -- conditions whose pathogenesis and microbial etiology are similar -- are based on the following points: (1) Acute otitis media is the most common infection for which antibiotics are prescribed in the United States. (2) As noted above, *S. pneumoniae* is the most likely treatable cause; taken together, *H. influenzae* and *M. catarrhalis*, many strains of which produceb-lactamases, are implicated nearly as frequently as pneumococci. (3) In the absence of diagnostic tympanocentesis, the etiologic diagnosis is nearly always presumptive. (4) Because penetration into a closed space is required, high serum levels of an effective antibiotic are required to treat otitis caused by intermediately or fully resistant pneumococci. (5) Otitis due to *S. pneumoniae* is more likely to fail to respond and to produce complications without specific therapy. (6) Antibiotics that are effective against pneumococci and yet resist b-lactamases tend to be very expensive compared with amoxicillin.

As a result of these considerations, theCDC's Otitis Media Working Group recommends that initial therapy be amoxicillin in a high dosage -- e.g., 80 mg/kg for infants and toddlers or 500 mg four times daily for adults. If this regimen fails, highly penicillin-resistant pneumococci orb-lactamase-producing bacteria may be responsible, and a course of cefpodoxime, perhaps preceded by a single parenteral dose of ceftriaxone, is recommended. Once therapy has begun, patients must be monitored closely for a response. Despite the detection (by molecular analysis) of pneumococcal DNA in middle-ear fluid, chronic serous otitis ("glue ear") is probably not due to active infection and does not require antibiotic therapy.

***Meningitis*** A reasonable recommendation is that pneumococcal meningitis be treated initially with cefotaxime (2 g every 6 h) or ceftriaxone (1 to 2 g every 12 h) plus vancomycin (500 mg every 6 h or 1 g every 12 h). Two drugs are given initially because the cephalosporin is likely to be effective against most isolates and readily penetrates the blood-brain barrier, whereas vancomycin is uniformly effective but has a somewhat unpredictable capacity to cross the blood-brain barrier. If the isolate is shown to be penicillin-susceptible, treatment can be continued with 24 million units of penicillin every 24 h, given every 4 h in divided doses or continuously. If the isolate exhibits reduced susceptibility to penicillin but is susceptible to cefotaxime or ceftriaxone, the administration of vancomycin may be discontinued. Rifampin inhibits the bactericidal activity ofb-lactam antibiotics and probably should not be added to the regimen. The total duration of therapy for pneumococcal meningitis is 10 to 14 days. Despite the central pathogenic role of inflammation in meningitis, the use of glucocorticoids or other anti-inflammatory agents is controversial, even in children, in whom most of the relevant studies have been done. Data simply do not exist on which to base an informed

decision regarding the administration of glucocorticoids or cyclooxygenase inhibitors to adults with pneumococcal meningitis (Chap. 372). Meningitis should be treated in an intensive care unit and with the participation of appropriate consultants, generally including a neurologist and a specialist in infectious diseases.

***Endocarditis*** Pneumococcal endocarditis is associated with rapid destruction of heart valves. Vancomycin should be given pending assays for the minimal bactericidal concentrations of b-lactam antibiotics. There is no clear evidence that the addition of another antibiotic to the regimen is beneficial; aminoglycosides are somewhat synergistic and rifampin or quinolones are antagonistic with b-lactams. Endocarditis and meningitis should be treated initially in an intensive care unit, with the participation of appropriate consultants. Patients with endocarditis should probably be treated in collaboration with an infectious disease consultant, a cardiologist, and a cardiovascular surgeon.

**Other Therapeutic Modalities** A variety of agents that block the action ofTNF-a,IL-1, or platelet-activating factor have conferred no benefit in and may have had a detrimental effect on pneumococcal sepsis. Similar results have been obtained with glucocorticoids.

## PREVENTION

Pneumococcal vaccine contains 25 ug of capsular polysaccharide from the 23 most prevalent serotypes of *S. pneumoniae*; vaccination stimulates antibody to most serotypes in most recipients. In adults under 55 years old, protection rates are at least 85%, even 5 years or longer after vaccination. The level and duration of protection decrease with advancing age, perhaps because of a diminished avidity of the antibody for the capsular polysaccharide. As a result, persons in their eighties have 50% protection for 3 years and very little or no protection thereafter. In subgroups of the population at high risk (e.g., debilitated elderly persons and individuals with severe chronic lung disease), vaccine has not been shown conclusively to be effective. Persons who most need the vaccine because of poor IgG responses are not likely to respond to immunization with significant increases in antibody level. Nevertheless, the poor average rate of response should not deter the physician from administering vaccine to individual patients who are at increased risk of pneumococcal infection. In light of the safety, low cost, and efficacy of vaccine and the emergence of antibiotic-resistant strains, the failure to vaccinate elderly persons and individuals who have conditions predisposing to pneumococcal disease is viewed by some authorities as a missed opportunity in public health policy.

TheCDC's Immunization Practices Advisory Committee has broadened its recommendations for pneumococcal vaccination to include all persons over the age of 2 years who are at substantially increased risk of developing pneumococcal infection and/or a serious complication of such an infection. General categories included within these recommendations are as follows: (1) persons over the age of 65; (2) persons with anatomic or functional asplenia,CSFleak, diabetes mellitus, alcoholism, cirrhosis, chronic renal insufficiency, chronic pulmonary disease, or advanced cardiovascular disease; (3) persons who have an immunocompromising condition associated with increased risk of pneumococcal disease, such as multiple myeloma, lymphoma, Hodgkin's disease, HIV infection, organ transplantation, or chronic use of

glucocorticoids; (4) persons who are genetically at increased risk, such as Native Americans and Alaskans; and (5) persons who live in special environments where outbreaks are particularly likely to occur, such as nursing homes. This list should not be regarded as all-inclusive.

Recommendations regarding revaccination seem to be somewhat inconsistent. A single revaccination is advocated for persons over the age of 65. Since antibody levels decline and there is no anamnestic response, it seems more reasonable simply to recommend revaccination at 5-year intervals, especially in persons over the age of 65, who tend to have almost no local reaction, and in splenectomized patients, who are most in need. If penicillin-resistant pneumococci continue to increase in prevalence, routine immunization of children over the age of 2 years should be considered. Pneumococcal vaccine has not been useful in children<2 years of age, who do not respond well to polysaccharide antigens. In a recent field trial, a heptavalent protein-conjugate pneumococcal polysaccharide vaccine protected infants and children against pneumococcal pneumonia, bacteremia, and meningitis; this vaccine is likely to be released for administration to young children in the next few years.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 139. STAPHYLOCOCCAL INFECTIONS - *Jeffrey Parsonnet*, *Robert L. Deresiewicz*

The staphylococci are hardy and ubiquitous colonizers of human skin and mucous membranes and were among the first human pathogens identified. They cause a variety of syndromes, including superficial and deep pyogenic infections, systemic intoxications, and urinary tract infections. Staphylococci are the leading cause of bacteremia, surgical wound infections, and infections of bioprosthetic materials in the United States; in addition, they are the second leading cause of nosocomial infections. Organisms of this genus are also a significant cause of bacterial food poisoning.

*Staphylococcus aureus* is the most important human pathogen in the genus. It remains a major public health concern due to its tenacity, potential destructiveness, and increasing resistance to antimicrobial agents. Although less virulent, the coagulase-negative staphylococci (CoNS), especially *S. epidermidis*, adhere avidly to prosthetic materials and are important nosocomial pathogens, especially of compromised hosts. Another CoNS species, *S. saprophyticus*, is a common cause of urinary tract infections.

### TAXONOMY AND MICROBIOLOGY

Members of the genus *Staphylococcus* are nonmotile, nonsporulating gram-positive cocci, 0.5 to 1.5 um in diameter, that occur singly and in pairs, short chains, and the irregular three-dimensional clusters from which their name is derived (Greek *staphule,* "grape-like"). Staphylococci can grow over a wide range of environmental conditions, but they grow best at temperatures between 30°C and 37°C and at a pH around neutrality. They are resistant to desiccation and to chemical disinfectants, and they tolerate NaCl concentrations up to 12%. With rare exceptions, the staphylococci are facultatively anaerobic. The more virulent staphylococci can clot plasma (coagulase-positive), while the less virulent cannot (coagulase-negative). Of the six recognized coagulase-positive staphylococcal species, the only important human pathogen is *S. aureus*, whose colonies are larger than those of *S. epidermidis*, are often pigmented (golden yellow), and are usuallyb-hemolytic on sheep blood agar. Twenty-eight species of CoNSare recognized. Of these, *S. epidermidis* is by far the most common nonurinary human isolate. Strains of *S. epidermidis* are typically white and nonhemolytic and may be tenaciously adherent as a result of their production of polysaccharide adhesin. *S. epidermidis* is followed in frequency by *S. hominis*, *S. haemolyticus*, and *S. warneri*. *S. lugdunensis* is increasingly recognized as a cause of serious human infection. *S. saprophyticus* is the most common staphylococcal urinary isolate.

## *STAPHYLOCOCCUS AUREUS*

### EPIDEMIOLOGY

Humans constitute the major reservoir of *S. aureus* in nature. The mucous membranes of the anterior nasopharynx are the principal site of carriage, with roughly 30% of healthy adults being so colonized at any point in time. Other common sites of colonization include the axillae, the vagina, damaged skin, and the perineum. Among postmenarcheal U.S. women, the rate of vaginal colonization by *S. aureus* ranges from

5 to 15% but rises to 30% during menses -- a change that is relevant to the pathogenesis of the toxic shock syndrome (TSS). Most adults are colonized by *S. aureus* intermittently, whereas 10 to 20%have persistent colonization and about the same percentage are never found to harbor the organism. Colonization is influenced by both microbial and host factors as well as by the nature of the competing nonstaphylococcal flora. Carriage is more common among persons with frequent staphylococcal exposure and those with habitual or chronic disruption of cutaneous epithelial integrity. Thus, colonization rates are higher among health care workers, dialysis patients, patients with type 1 diabetes, injection drug users, persons infected with HIV, and individuals with chronic dermatologic conditions. After 2 weeks in a hospital, colonization rates rise to 30 to 50%, and colonizing strains are more likely to be resistant to antibiotics.

Colonization of mucocutaneous sites is an important risk factor for staphylococcal infection. For example, surgical wound infection following cardiothoracic surgery is up to 10 times more likely among patients who harbor *S. aureus* in the nares preoperatively than among those who do not. The vast majority of postoperative wound infections of all types are caused by a strain of *S. aureus* that was present in the nares before surgery. Furthermore, presurgical clearance of carriage with topical and systemic antibiotics decreases the incidence of postoperative staphylococcal infection, but it is not yet standard practice to screen and treat patients before surgery.

## PATHOGENESIS AND HOST DEFENSE

*S. aureus* causes two types of syndrome: *intoxications* and *infections*. The clinical manifestations of intoxications are attributable to the action of one or a few secreted products of the microorganism (toxins), and these clinical features can be reproduced by administration of the toxin(s) in the absence of the microorganism. The toxin can be produced either in vivo (as inTSS or staphylococcal scalded skin syndrome) or in a suitable vector that subsequently delivers it to the host (as in staphylococcal food poisoning). Infections, in contrast, involve bacterial proliferation, invasion or destruction of host tissues, and -- in most cases -- local and systemic inflammatory responses by the host to these events. The ability of a microorganism to infect is predicated on its ability to produce certain products that enable it to survive and prosper in the host (*virulence factors*), and *S. aureus* is particularly well-armed in this regard.

**Steps in Pathogenesis** The pathogenesis of staphylococcal intoxications is straightforward and involves four steps: colonization by a toxigenic strain of the bacterium, toxin production, toxin absorption, and intoxication. The pathogenesis of invasive infections is more complex and the steps are less discrete. They include colonization, invasion of the bacterium across epithelial or mucosal barriers, adherence to materials in the extracellular matrix, evasion or neutralization of host defenses, and destruction of host tissues. For both intoxications and infections, the entire process is carefully orchestrated by the bacterium in response to specific environmental conditions.

*Physical Preservation of Cellular Integrity* Staphylococci are robust and adaptable organisms that can survive under relatively harsh environmental conditions. A rigid cell wall confers shape and strength to the organisms. The major component of the cell wall, *peptidoglycan*, is responsible for its physical properties. Disruption of peptidoglycan

cross-linking by cell wall-active antibiotics (b-lactams or glycopeptides) renders staphylococci susceptible to lysis mediated by endogenous peptidoglycan hydrolases (*autolysins*). The osmotolerance exhibited by *S. aureus* enables the organism to grow without microbial competition in foods of low water activity and so sets the stage for contamination of food by staphylococcal enterotoxins (SEs), which cause food poisoning.

*Colonization* Staphylococcal colonization of the nasal mucosa is mediated by adherence of cell-surface components to host molecules (e.g., mucin carbohydrate). Factors contributing to colonization of other surfaces, such as the vaginal mucosa, are poorly understood. After colonization, the production of certain staphylococcal toxins [toxic shock syndrome toxin 1 (TSST-1), exfoliative toxins, orSEs] can ensue under the appropriate environmental conditions. Colonization may be transient or persistent; the latter condition increases the likelihood that organisms will gain access to deeper tissues, beginning the process of infection.

*Invasion and Adherence to the Extracellular Matrix* Staphylococci generally cannot invade through intact epithelial surfaces, which represent the primary line of antistaphylococcal defense. Invasion is facilitated by a mechanical break in the epithelium or by plugging of a gland or hair follicle. Once the epithelial barrier is breached, colonization of host tissues is facilitated by adherence of *S. aureus* to molecules present either on host cell surfaces or in the extracellular matrix. Several staphylococcal surface proteins, including protein A, function as adhesins by binding extracellular matrix molecules. These proteins have been designated "microbial-surface components recognizing adhesive matrix molecules" and may adhere to fibrinogen, fibronectin, collagen, elastin, and other serum constituents.

*Destruction of Host Cells and Alteration of the Host Microenvironment* A number of products of *S. aureus* alter the host environment in a way that benefits the bacterium. *Coagulase* is a secreted enzyme that binds prothrombin and thereby causes the conversion of fibrinogen to fibrin; it may aid in the establishment of an environment within host tissues that is protected from cells of the immune system or from antibiotics. *S. aureus* produces a number of *lipases*, which may enhance the organism's survival in sebaceous areas of the human body. *Hyaluronidase* hydrolyzes hyaluronic acid, a mucopolysaccharide present in extracellular ground substance; its action may facilitate the spread of the organism through the extracellular matrix to adjoining tissues. *Staphylokinase*, *thermonuclease*, and *serine protease* are other extracellular enzymatic products that may play roles in pathogenesis.

*S. aureus* produces a number of membrane-active toxins that probably contribute to pathogenesis by damaging host cells, although their exact role in pathogenesis remains uncertain. These toxins include a-,b-, and d-hemolysins and the synergohymenotropic toxins (g-hemolysin and Panton-Valentine leukocidin).*a-Hemolysin* (a-toxin) is the prototypic pore-forming toxin; it inserts into the cell membrane, creating ion-conductive channels that destroy membrane integrity. The toxin is dermonecrotic on subcutaneous injection, induces proinflammatory changes in mammalian cells, and -- in animal models -- induces many findings seen in sepsis, including hypotension and thrombocytopenia. The *synergohymenotropic toxins* are a family of bicomponent toxins. Their name derives from the fact that their two components are tropic for cell membranes and are

synergistically active against them. Like a-toxin, the synergohymenotropic toxins are pore-forming toxins. *Panton-Valentine leukocidin* is most active against polymorphonuclear cells, monocytes, and macrophages. It is dermonecrotic to rabbit skin, and strains producing it are strongly associated with human furunculosis.

*Evasion of Host Defense* Once staphylococci have breached mucosal or epithelial barriers, the host's immune response is directed at containing and eliminating them, principally by polymorphonuclear recruitment and phagocytic killing. The bacteria fight back by cloaking antigenic determinants on their surface, by interfering with the function of opsonins, by directly killing the phagocytes, and by developing strategies to survive within them. The pyogenic abscess, the histologic hallmark of staphylococcal infection, represents the battlefield for this encounter, in which the microorganism survives in an environment in which leukocyte function is impaired and into which antibiotics penetrate poorly. Although the abscess may contain the spread of the bacteria, patients with abscesses are symptomatic and usually require surgical drainage for relief.

Some staphylococcal components and products are direct chemoattractants for polymorphonuclear leukocytes; others provoke the release of chemoattractant cytokines that recruit phagocytic cells to the infected area. Histologic sections of early lesions typically reveal a central focus of organisms surrounded by a zone of necrotic debris, which in turn is surrounded by a zone of viable inflammatory cells. The toxic action of staphylococcal leukocidin may in part explain the zone of necrosis. After several days, fibroblasts populate the margin of the abscess and there elaborate collagen, which creates a true capsule around the abscess.

Staphylococcal cell-wall peptidoglycan activates complement, which is an important opsonin in persons lacking antibody to staphylococcal surface components. Peptidoglycan also acts as a general stimulator of inflammatory cytokine release and may thereby contribute to sepsis, but it is weaker in this regard than gram-negative lipopolysaccharide. Opsonic antibodies specific for peptidoglycan or capsule mediate phagocytosis by polymorphonuclear leukocytes and macrophages in vitro, although the role of antibody in vivo is less certain. There is considerable interstrain variation in susceptibility to opsonization, and acquired protective immunity to staphylococcal infection is generally thought *not* to develop. (In contrast, acquired antibody-mediated immunity to systemic staphylococcal intoxications does occur; e.g.,>90% of healthy adults have protective antibody to the most commonTSStoxin,TSST-1.) Mitigating against opsonization is *protein A*, an important cell-surface component; protein A binds the Fc portion of IgG subclasses 1, 2, and 4 and thereby interferes with antibody-mediated opsonization. Polysaccharide capsule, which is produced by most clinical isolates, may also interfere with opsonization.

*S. aureus* has numerous defenses against killing after phagocytosis. Intracellular bacteria are usually killed rapidly by the oxidative burst within the phagosome, but staphylococcal catalase, which converts hydrogen peroxide to oxygen and water, detoxifies oxygen radicals and potentiates intracellular survival. Staphylococci are also taken up by nondedicated phagocytes, such as endothelial cells and osteoblasts, and may survive within them. One strategy for intracellular survival is the genesis of small-colony variants (SCVs). These slow-growing cells exhibit alterations in electron transport and generally produce reduced amounts of virulence determinants such as

a-toxin and coagulase. They are relatively resistant to cell wall-active antibiotics and aminoglycosides and are capable of persisting intracellularly for extended periods, thereby evading host defenses. Their slow growth also makes them less likely to be recovered in the clinical laboratory and then targeted for treatment. Their existence may in part explain the startling capacity of certain *S. aureus* infections (e.g., chronic osteomyelitis) to recrudesce after years of dormancy and the difficulty of curing infections in intravascular sites and bone. Prolonged exposure to aminoglycosides or to trimethoprim-sulfamethoxazole appears to be a risk factor for the development of SCVs.

Hosts at particular risk for staphylococcal infection include those with frequent or chronic disruptions in epithelial or mucosal integrity; those with disordered leukocyte chemotaxis, such as patients with the Chediak-Higashi or Wiskott-Aldrich syndrome; those whose phagocytes are defective in oxidative killing, as in chronic granulomatous disease; those with neutropenia or acquired functional deficiencies (e.g., deficiencies induced by exogenous glucocorticoids); and those with indwelling foreign bodies, which provide a matrix for staphylococcal adherence and biofilm formation and seriously impair phagocytic function. Patients with disorders of immunoglobulin or complement (especially C1-C4 deficiencies) are also at increased risk for *S. aureus* infection.

**Superantigens** The superantigens are $V_b$-restricted T cell mitogens: they bind directly and without prior processing to major histocompatibility class II molecules on the surface of antigen-presenting cells, thereby stimulating T cells on the basis of the sequence of the variable region of the b chain of the T cell receptor rather than on the basis of the epitope specified by this receptor. Accordingly, a superantigen may be able to stimulate>10% of the T cells in a given individual -- a percentage much higher than the ~1 in $10_6$cells stimulated by conventional antigens. This massive T cell stimulation provokes an exuberant and dysregulated immune response characterized by the release of the cytokines interleukins 1 and 2, tumor necrosis factor, and interferon g.TSS is a manifestation of this process, as some aspects of septic shock may be as well. *S. aureus* produces a number of superantigens, including theSEs,TSST-1, and possibly the exfoliative toxins (ETs). Ten SEs have been identified to date, several of which are common causative agents of staphylococcal food poisoning. The mechanism by which the SEs cause vomiting is uncertain but may involve direct neural stimulation of the autonomic nervous system rather than a local effect on the gastrointestinal mucosa. The superantigenic properties of TSST-1 and the SEs are thought to explain their ability to cause TSS, although the exact mechanism by which they craft the various clinical manifestations of TSS is uncertain. There is conflicting evidence as to whether theETs, which cause scalded skin syndrome, are superantigens; structural data suggest that they may instead be related to the serine proteases.

**Genetic Regulation of Virulence Genes** The production of virulence factors by bacteria is typically tightly and coordinately regulated by genetic apparatuses that sense and respond to environmental cues. Such coordinate regulation enables an organism to rapidly tailor its repertoire of proteins to suit its changing needs, either as it passes between microenvironments or as the environment evolves around it. Many of the staphylococcal exoproteins are typical virulence factors in this regard. For example, a-, b-, andd-hemolysins,TSST-1, staphylococcal enterotoxin B, serine protease, and thermonuclease are all produced during the late logarithmic phase of growth in batch culture, at a time when nutrients become scarce and cell density reaches saturation.

Their production is coordinately regulated and occurs reciprocally to that of the cell wall-associated staphylococcal proteins protein A and coagulase. Several genetic regulatory loci modulate these events, as do specific environmental conditions that presumably operate through those genetic loci. Foreign materials that increase the risk ofTSS and conditions in food that predispose to staphylococcal food poisoning probably do so by presenting microenvironments that stimulate production of the relevant toxins. Similar events are undoubtedly operative within the environment of host tissues during infection, even in the absence of a foreign body.

Several distinct genetic loci regulate exoprotein production in *S. aureus*, the best-studied of which are *agr* (accessory gene regulator) and *sar* (staphylococcal accessory regulator). Both affect gene expression primarily at the level of transcription, and both activate the expression of secreted proteins and diminish the expression of cell wall-associated proteins during the late logarithmic phase of bacterial growth. Data suggest that *agr* may function primarily as a "quorum sensor," an apparatus that informs the bacterium of the density of staphylococci in its environment. Exoprotein regulation in *S. aureus* apparently results from a complex interplay of environmental factors and gene products.

## STAPHYLOCOCCAL INTOXICATIONS

**Toxic Shock Syndrome** TSS is an acute, life-threatening intoxication characterized by fever, hypotension, rash, multiorgan dysfunction, and desquamation during the early convalescent period (Fig. 139-1,Fig. 139-CD6). The disease was first characterized in 1978 but gained notoriety in 1980 upon the recognition of many cases among menstruating women. It is a relatively uncommon illness, with a reported annual incidence (among menstruating women) of 1 case per 100,000; it is likely, however, that the disease is substantially underreported, especially nonmenstrual cases. About half of all cases occur in settings other than menstruation and are distributed among individuals of both sexes and all ages. Menstrual and nonmenstrual cases are clinically indistinguishable. Among cases reported to the Centers for Disease Control and Prevention between 1985 and 1994, the minimum case-fatality rate was 2.5% for menstrual cases and 6.4% for nonmenstrual cases.

TSSis caused by any of several related exoproteins produced by *S. aureus*.TSST-1is the toxin most frequently implicated (causing virtually all menstrual cases), and staphylococcal enterotoxin B is the second most frequent. For illness to develop, an individual must be colonized or infected with a toxigenic strain of *S. aureus* and must lack a protective level of antibody to the toxin made by that strain. That TSS is primarily a disease of the young reflects the fact that >90% of adults have antibodies to TSS toxins.

Menstruation remains the most common setting forTSS, but the disease can also complicate the use of barrier contraceptives and childbirth. Moreover, nonmenstrual TSS can ensue after superinfection of skin lesions of many types, including burns, insect bites, varicella lesions, and surgical wounds. Postoperative disease can develop from hours to weeks after any surgical procedure. Staphylococcal superinfection after influenza is a common setting for TSS, as is acute sinusitis. Overt infection with *S. aureus* is not required for the development of TSS; mere colonization with a toxigenic

strain may suffice. Accordingly, the primary site of toxin production in TSS may appear entirely benign.

TSSremains a clinically defined syndrome (Table 139-1). Patients meeting the case definition are severely ill, although milder forms of "staphylococcal toxin-mediated disease" do occur. The illness usually begins precipitously, with high fever and a complex of symptoms that may include nausea, vomiting, abdominal pain, diarrhea, muscular pain, sore throat, and headache. Dizziness is common as a manifestation of orthostatic or frank hypotension. The characteristic macular erythroderma develops over the first 2 days of illness. It is usually generalized but is sometimes locally confined; it can be evanescent or persistent. The patient's mental status is often abnormal to a degree that is out of proportion to the degree of hypotension. Conjunctival suffusion (Fig. 18-CD3), pharyngeal injection, and peripheral edema are evident in many cases; a so-called strawberry tongue develops in up to half of patients. In menstrual disease, the vaginal mucosa may be erythematous and a purulent vaginal discharge may be present, but these findings are not universal. Common laboratory abnormalities include azotemia, hypoalbuminemia, hypocalcemia, hypophosphatemia, creatine phosphokinase elevation, leukocytosis or leukopenia with a left shift, thrombocytopenia, and pyuria.

The early signs and symptoms ofTSSresolve within the first few days of illness, after which complications of organ hypoperfusion, such as renal and myocardial dysfunction, fluid overload, and adult respiratory distress syndrome, dominate the picture. After about a week of illness, desquamation begins with superficial flaking of the skin of the torso, face, and extremities, which may be followed by full-thickness desquamation of the palms, soles, and digits. Common late sequelae include peripheral gangrene, reversible nail and hair loss, muscle weakness, and lingering asthenia and neuropsychiatric dysfunction.

The differential diagnosis ofTSS is that of a severe febrile exanthem with hypotension. In the setting of menstruation accompanied by purulent vaginal discharge, the diagnosis may be obvious. The challenge is to recognize the less obvious cases, in which the exanthem may be fleeting, multiorgan dysfunction may be subtle, or (in nonmenstrual cases) a primary site of infection may be inapparent. Recovery of *S. aureus* supports the diagnosis, as does demonstration of toxin production by the strain and serologic susceptibility to the toxin. Other diagnoses to consider include streptococcal TSS, staphylococcal scalded skin syndrome, Kawasaki syndrome, Rocky Mountain spotted fever, leptospirosis, meningococcemia, gram-negative sepsis, exanthematous viral syndromes, and severe drug reactions. Staphylococcal TSS and streptococcal TSS (Chap. 140) can be clinically indistinguishable.

Treatment ofTSSinvolves drainage of the site of toxin production, aggressive fluid resuscitation, and administration of antistaphylococcal antibiotics. Recent surgical wounds should be explored and irrigated, even when signs of inflammation are lacking; foreign bodies should be removed. Pressors should be used for sustained hypotension that is unresponsive to fluids. Electrolyte abnormalities, particularly hypocalcemia and hypomagnesemia, must be corrected. Penicillinase-resistant penicillins (nafcillin, oxacillin) and first-generation cephalosporins have been widely used in TSS. A growing body of clinical and laboratory evidence indicates, however, that a protein synthesis

inhibitor, such as clindamycin, might be superior to b-lactam agents. The authors recommend therapy with clindamycin (900 mg intravenously every 8 h), either alone or in combination with a b-lactam antibiotic [or vancomycin for patients perceived to be at risk for infection with methicillin-resistant *S. aureus* (MRSA)]. For a seriously ill patient in whom the diagnosis of TSS is uncertain, broad-spectrum antibiotics may be appropriate until the diagnosis is confirmed. A 14-day course of therapy -- some of which may be administered perorally -- is reasonable. Patients whose illness is severe enough to warrant vasopressors, who require mechanical ventilation, who have worsening renal function, or who have an undrainable focus of infection should be treated with intravenous immunoglobulin, which contains high levels of neutralizing antibody to TSS toxins. A single infusion of 400 mg/kg generates a protective level of antibody toTSST-1that persists for weeks. Glucocorticoids have not been shown to be of significant benefit.

Because vaginal staphylococcal carriage can be persistent or recurrent and because in more than half of all casesTSS does not elicit immunity, recurrent menstrual TSS is a concern; recurrent nonmenstrual TSS has also been reported. The risk of recurrent illness can be assessed by tests for seroconversion toTSST-1. Women who do not seroconvert after acute illness (or who are not tested for antibody) should refrain indefinitely from using tampons or barrier contraceptives.

**Staphylococcal Scalded Skin Syndrome** This syndrome encompasses a range of cutaneous diseases of varying severity caused byET-producing strains of *S. aureus*. The most severe form of staphylococcal scalded skin syndrome is termed *Ritter's disease* in newborns and *toxic epidermal necrolysis* (TEN) (Fig. 18-CD5) in older individuals. Milder and more common forms include *pemphigus neonatorum* and (in children and adults) *bullous impetigo* (see "Skin and Soft Tissue Infections," below). Persons>5 years old rarely develop staphylococcal TEN; those who do almost invariably have underlying disease (renal insufficiency, systemic immunosuppression). The rarity of the syndrome in adults has been ascribed to acquired immunity to the inciting toxins, to enhanced renal clearance of the toxins, and perhaps to diminished sensitivity to the action of the toxins.

StaphylococcalTEN, or Ritter's disease, often begins with a nonspecific prodrome. The acute phase starts with the onset of an erythematous rash. The erythema begins in the periorbital and perioral areas and spreads to the trunk and centrifugally to the limbs. Pastia's lines may be apparent. The skin has a sandpaper texture and is often tender. Periorbital edema is common. In infants and children, fever and irritability or lethargy are common, but systemic toxicity is not. Within hours or days, wrinkling and sloughing of the epidermis begin; sloughing can be provoked by gentle stroking of the skin (Nikolsky's sign), even in areas that appear uninvolved. The denuded areas are red and glistening but not purulent, and staphylococci are not present. Exfoliation may continue in large sheets or in ragged snippets of tissue. Large, flaccid bullae may develop. As in thermal burns, significant fluid and electrolyte loss can occur at this stage, as can secondary infection. Within about 48 h, the exfoliated areas dry and secondary desquamation begins. The entire illness resolves within about 10 days. Mortality (from hypovolemia or sepsis) is ~3% among children but approaches 50% among adults. Treatment includes the administration of antistaphylococcal agents, fluid and electrolyte management, and local care to the denuded skin.

**Staphylococcal Food Poisoning** Between 2 and 6 h after ingestion of contaminated food, staphylococcal food poisoning begins abruptly with nausea, vomiting, crampy abdominal pain, and diarrhea. The diarrhea is usually noninflammatory and is of lower volume than that in cholera or toxigenic *Escherichia coli* infection. Fever and rash are absent, and the patient is neurologically normal. The majority of cases are self-limited and resolve between 8 and 24 h after onset. In severe cases, hypovolemia and hypotension can develop. Although most cases probably do not come to medical attention and are not diagnosed, staphylococcal intoxication is the second or third leading cause of diagnosed food poisoning in the United States.

Food poisoning is caused by the ingestion of any of theSEs, which are produced by *S. aureus* in contaminated food before it is eaten. The presence of SEs in the food vector before its consumption accounts for the short incubation period of this illness. The SEs are heat stable, thus tolerating cooking conditions that kill the organisms that produced them. The disease has a high attack rate and is somewhat more common during the summer than at other times of the year. Processed meats and custard-filled baked goods are common food vectors, perhaps because staphylococci can tolerate conditions of high protein, salt, or sugar and so grow without competition in these environments. The most important epidemiologic risk factor in outbreaks of this disease is the ingestion of food that has been left at warm temperatures for prolonged periods, thereby allowing toxin production to occur before consumption. Contaminated preparation equipment and poor personal hygiene of food handlers are frequently implicated as well.

## STAPHYLOCOCCAL INFECTIONS

*S. aureus* causes invasive disease by breaching host defense barriers, often after disruption or dysfunction of such barriers. The most common portals of entry leading to staphylococcal invasion are the skin and associated structures. A nidus for staphylococcal colonization and subsequent invasion is provided by chronic skin conditions, such as eczema and psoriasis; acute breaks in the skin, such as puncture wounds (Fig. 139-CD1), abrasions, and lacerations; and abnormalities of skin appendages, such as hair follicles and nails (Fig. 139-CD2). Colonization of the nasopharynx predisposes to respiratory tract infection after aspiration, obstruction (e.g., of a bronchus by carcinoma or of sinus ostia by trauma, edema, or polyps), or impaired ciliary function (e.g., in chronic bronchitis or acute viral infection). Intubation of the trachea provides a conduit by which upper respiratory flora, including pathogens such as *S. aureus*, can reach the lower respiratory tract.

**Skin and Soft Tissue Infections** *S. aureus* is the most common etiologic agent of skin and soft tissue infections (Chap. 128). Such infections are usually caused by endogenous flora -- i.e., strains of *S. aureus* that are harbored in the nares or other sites of colonization. Infection may represent a primary pathologic process, with direct invasion of skin and adjacent tissues, or a secondary process complicating preexisting lesions.

Staphylococcal infections originating in hair follicles range in severity from trivial to life-threatening. *Folliculitis* (Fig. 128-CD3) is an infection of follicular ostia; the

appearance is that of a domed yellow pustule with a narrow red margin. Infection is often self-limited, although healing may be hastened by topical antiseptics and more severe cases may benefit from topical or systemic antibiotics. A *furuncle* (often called a *boil*;Fig. 139-CD3) is a deep-seated necrotic infection of a hair follicle, most often located on the buttocks, face, or neck. Furuncles are painful and tender, and their appearance is often accompanied by fever and constitutional symptoms. Surgical drainage and systemic antibiotic treatment may hasten recovery and limit scar formation. Deep infection of a group of contiguous follicles is called a *carbuncle* (Fig. 139-CD4). This type of painful necrotic lesion occurs most commonly on the back of the neck, shoulders, hips, and thighs, typically in middle-aged or elderly men. There is intense inflammation of surrounding and underlying connective tissue, and the infection may be complicated by bacteremia. Surgical drainage and systemic antibiotic administration are indicated. *S. aureus* is also the most common cause of acute *paronychia*, infection of the lateral nail folds.

*S. aureus* causes *bullous impetigo* (Fig. 128-CD1), a superficial cutaneous disorder occurring predominantly in children. An epidermal split caused byETresults in the formation of 1- to 2-cm bullae containing neutrophils and organisms. *Nonbullous impetigo* is most often caused byb-hemolytic streptococci, but *S. aureus* can secondarily infect impetiginous lesions. Treatment of impetigo with a topical antibiotic, such as mupirocin, may suffice for mild and localized infection, whereas systemic therapy is indicated for widespread or severe disease or for infection accompanied by lymphadenopathy.

*Cellulitis*, a spreading infection of subcutaneous tissue, is occasionally caused by *S. aureus* (Fig. 139-CD5), butb-hemolytic streptococci are more common agents of this disease (Chap. 140). Secondary infection of surgical and traumatic wounds is more likely to be staphylococcal in etiology than is cellulitis arising from minor or inapparent breaks in the skin, and empiric treatment directed against both *S. aureus* and streptococci is reasonable in these settings. *Erysipelas*, the hallmark of which is a well-demarcated raised border, is a more superficial infection of the dermis and subcutaneous tissue; it is usually caused by group A streptococci and only rarely, if ever, by *S. aureus*.

**Respiratory Tract Infections** *S. aureus* can gain access to the lung parenchyma by two routes: aspiration of upper respiratory flora and hematogenous spread. Staphylococcal pneumonia is a relatively uncommon but severe infection, characterized clinically by chest pain, systemic toxicity, and dyspnea and pathologically by intense neutrophilic infiltration, necrosis, and abscess formation. *Pleural empyema* is a common complication and increases the already-considerable morbidity associated with this infection. Only rarely does *S. aureus* cause pneumonia without predisposing epidemiologic or host factors that favor colonization of the respiratory tract and/or that impair defense mechanisms. Residence in a chronic care facility, recent use of antibiotics, and hospitalization favor colonization -- and hence respiratory tract infection -- with *S. aureus*. Staphylococcal pneumonia most commonly follows tracheal intubation of a hospitalized patient or viral infection of the respiratory tract. Influenza virus is known both to increase respiratory colonization by *S. aureus* and to impair ciliary function (and therefore clearance of staphylococci). In a classic scenario, a patient (often elderly and/or institutionalized) develops a flulike respiratory illness and then, after several

days, deteriorates rapidly, with high fever, dyspnea, productive cough, and obtundation. The diagnosis of staphylococcal pneumonia is readily established by Gram's staining of expectorated sputum, which reveals abundant clusters of gram-positive cocci.

Hematogenous seeding of the lungs with *S. aureus* follows embolization from an intravascular nidus of infection. Common settings for septic pulmonary embolization are right-sided endocarditis (especially common among injection drug users) and septic thrombophlebitis, which is most often a complication of an indwelling venous catheter. Pneumonia is heralded by the acute onset of pleuritic chest pain and dyspnea; although diagnostic sputum may be lacking, a chest radiograph typically shows multiple nodular infiltrates, providing an important clue to both the diagnosis and the pathogenesis of disease.

Although not typically considered in the differential diagnosis of sore throat, *S. aureus* is occasionally isolated as the dominant organism from patients (especially children) with exudative *pharyngitis*. The illness may be accompanied by a scarlatiniform rash and may result in systemic toxicity (like that seen inTSS). Staphylococcal *tracheitis* may be diagnosed in children who have systemic toxicity and positive respiratory cultures but who lack pulmonary infiltrates. *S. aureus* is a prominent cause of *chronic sinusitis*, typically following the selection pressure of antimicrobial regimens that lack activity against this organism. Finally, *S. aureus* is a major etiologic agent of *sphenoid sinusitis*.

**Infections of the Central Nervous System** *S. aureus* gains access to structures of the central nervous system by hematogenous spread or by direct extension from contiguous structures. This organism is a prominent cause of *brain abscess*, especially as a result of embolization during mitral or aortic valve endocarditis. Such abscesses are often multiple, small, and scattered diffusely throughout the brain. Brain abscess can also develop by direct extension from frontoethmoid or sphenoid sinuses or from infected soft tissue after surgery or penetrating trauma. Patients with staphylococcal brain abscesses are more likely to have fever, meningismus, and other signs of infection than are patients with anaerobic bacterial or mixed-etiology brain abscesses. Purulent *meningitis* may accompany staphylococcal brain abscess or may develop during bacteremia in the absence of demonstrable abscesses.

*S. aureus* is the organism most likely to cause a variety of other space-occupying, suppurative intracranial infections. *Subdural empyema* usually develops by direct extension of osteomyelitis of the skull, after surgery or trauma, or in the setting of sinusitis. This condition may be accompanied by meningitis, epidural abscess, or intracranial phlebitis. The cardinal features of subdural empyema are fever, headache, vomiting, and signs of meningeal irritation. As the infection progresses, cerebral edema, often with infarction, may ensue and may be accompanied by alteration in mental status, seizures, and focal neurologic signs, which sometimes progress rapidly. The diagnosis should be suspected in any patient with meningeal signs and focal neurologic findings. Magnetic resonance imaging (MRI) is the diagnostic procedure of choice; lumbar puncture is contraindicated because of the danger of brainstem herniation. Early surgical drainage and treatment with an antibiotic that penetrates well into the central nervous system may be curative, although neurologic sequelae are not uncommon.

*S. aureus* is the most common cause of *spinal epidural abscess*, which develops most

often in association with vertebral osteomyelitis or diskitis. The diagnosis is suggested by some combination of fever, back pain, radicular pain, lower-extremity weakness, and bowel or bladder dysfunction, but the presentation is often subtle, resulting in delayed diagnosis. Patients may report only difficulty in walking or weakness, and objective findings may initially be lacking. The principal danger is the potential for necrosis of the spinal cord by compression and/or venous involvement. Early recognition of this condition is critical if long-term sequelae, such as paraplegia, are to be averted. AnMRI scan of the spine establishes whether or not an epidural collection is present. Fluoroscopy- or computed tomography (CT)-guided needle aspiration may confirm the diagnosis, but an open procedure offers a higher yield. Prompt surgical decompression by laminectomy is often required for preservation of neurologic function, although a trial of antibiotic therapy alone may be considered if no focal neurologic deficits are detected at the time of diagnosis. Any deterioration in neurologic status should prompt urgent surgical intervention. The pathogenesis of *intracerebral epidural abscess* is similar to that of subdural empyema, with staphylococcal infection usually following sinusitis, craniotomy, or trauma. Clinical manifestations reflect the anatomy of the underlying osteomyelitis plus the mass effect of the abscess, cerebral edema, and (often) secondary involvement of the subdural space. Emergent surgical drainage is usually required for cure.

Finally, *S. aureus* is the most common cause of *septic intracranial thrombophlebitis*, typically following sinusitis, mastoiditis, or soft tissue infection of the face. Clinical manifestations reflect the underlying condition and the anatomic structures in contiguity with the infected vein or sinus. Focal neurologic deficits, particularly of cranial nerve function, are characteristic of cavernous sinus thrombosis. Sagittal sinus thrombosis may be manifested by leg and arm weakness and by altered mental status; infections of the lateral and petrosal sinuses also produce characteristic clinical syndromes. Intracranial phlebitis may accompany epidural abscess, subdural empyema, and meningitis and is sometimes clinically indistinguishable from other types of intracranial infection.MRI is the diagnostic procedure of choice.

**Urinary Tract Infections** *S. aureus* is an uncommon cause of urinary tract infection. Ascending infection almost exclusively follows instrumentation of the bladder (e.g., cystoscopy or placement of an indwelling catheter). Under other circumstances, the presence of *S. aureus* in the urine, even in low numbers, suggests staphylococcal bacteremia and hematogenous seeding of the kidneys, with or without abscess formation; staphylococcal endocarditis should be considered in this setting.

**Endovascular Infections** *S. aureus* is the most common cause of acute bacterial *endocarditis* of both native and prosthetic valves (Chap. 126). The organism may infect previously normal valves. Staphylococcal endocarditis presents as an acute febrile illness, rarely of more than a few weeks' duration; complications such as meningitis, brain or visceral abscess, peripheral vascular embolization, valvular incompetence with heart failure, myocardial abscess, and purulent pericarditis have often developed by the time a patient seeks medical attention. The valves most commonly involved are the mitral and/or the aortic except among injection drug users, in whom infection of the tricuspid valve is most common.

The diagnosis of endocarditis is suggested by a heart murmur and the presence of

conjunctival hemorrhages, subungual petechiae, or purpuric lesions on the distal extremities; it is readily confirmed by demonstration of high-grade bacteremia and echocardiography showing valvular vegetations. Echocardiography also helps establish which valve(s) are infected, the degree of valvular dysfunction or destruction, the quality of left ventricular function, and the presence or absence of annular or myocardial abscess. Transesophageal echocardiography (TEE) is more sensitive than transthoracic echocardiography (TTE) in detecting vegetations and abscesses, but it is also more invasive. TEE need not be performed in all cases of proven or suspected endocarditis. This approach is useful, however, in the setting of persistent bacteremia or fever (to evaluate for abscess) and in anticipation of surgery if TTE has not been sufficiently informative.

Native valve staphylococcal endocarditis carries a high mortality rate (on the order of 40%) and mandates prompt initiation of antimicrobial therapy. In addition to blood cultures and echocardiography, evaluation may includeCT of the head and lumbar puncture if brain abscess or meningitis is suspected; a radionucleotide study if osteomyelitis is suspected; and abdominal CT if visceral abscess is suggested by abdominal pain or persistent fever or bacteremia. Indications for valve replacement are the same as those in endocarditis caused by other organisms: persistent bacteremia (beyond 5 to 7 days of therapy), valvular dysfunction resulting in heart failure, perivalvular or myocardial abscess, or recurrent embolization. Early consultation with a cardiothoracic surgeon is advisable in all cases because of the high proportion of patients with *S. aureus* endocarditis (around half) who develop one of these complications and therefore require valve replacement, often urgently. Once there is an indication for removal of an infected valve, nothing is gained and much can be lost by delaying surgery. *S. aureus* infection of a prosthetic valve (as an early or a late complication of valve replacement) almost always requires surgery for one of the above indications.

Right-sided endocarditis, which most often develops in association with injection drug use or venous catheterization, is frequently complicated by septic pulmonary emboli but otherwise carries a lower rate of serious complications than left-sided disease. Surgery is rarely required for right-sided infection. A relatively short course of parenteral combination therapy (2 weeks) may be curative, and the prognosis is relatively good.

The propensity of *S. aureus* to adhere to and infect damaged tissues makes it the foremost cause of endovascular infections other than endocarditis. Vascular infection is a consequence of hematogenous seeding of damaged vessels, especially large arteries with atheromatous plaques, resulting in the development of a mycotic aneurysm. It may also develop by spread from a contiguous focus of infection (e.g., after vascular surgery), often resulting in an infected pseudoaneurysm, or by contamination of an intravascular device, resulting in septic phlebitis. Staphylococcal infection of an atherosclerotic artery (most commonly the abdominal aorta or iliac arteries), which may be aneurysmal to begin with, is a potentially catastrophic event. Such infections are associated with high-grade bacteremia, may result in rupture and massive hemorrhage, and require surgical resection and bypass of the infected vessel. Septic phlebitis is also associated with high-grade bacteremia and systemic toxicity but is less likely than arteritis to result in rupture. Persistent bacteremia suggests the need for surgical removal of infected thrombus or vein, but the technical difficulty of such surgery may

warrant an attempt at cure with antibiotics and anticoagulants alone.

**Bacteremia** A classic clinical scenario is that of a patient presenting with *S. aureus* bacteremia but without a demonstrable primary site of infection. Even in the absence of a changing murmur, peripheral embolic lesions, or a diagnostic echocardiogram, the possibility of endocarditis must be considered carefully in this situation. It is often hard to differentiate between endocarditis and bacteremia arising from another primary site; in addition, *S. aureus* may secondarily seed endovascular sites, such as heart valves or atheromatous plaques. Several criteria increase the likelihood that a patient has endocarditis as opposed to simple bacteremia: community (vs. nosocomial) acquisition of infection, absence of an apparent primary site of infection, and evidence of metastatic infection. The evaluation of a bacteremic patient should be tailored to the individual but may include an abdominalCT scan and a bone scan or gallium scan to detect an occult visceral abscess or osteomyelitis.TEE has demonstrated valvular abnormalities suggestive of endocarditis in up to one-fourth of bacteremic patients who lack clinical orTTEevidence of endocarditis. This finding has prompted some authorities to recommend TEE for all patients with staphylococcal bacteremia. The authors favor performance of this test for patients with persistent fever or bacteremia.

Complications of *S. aureus* bacteremia include abscesses of abdominal viscera, brain abscess, meningitis, septic arthritis, osteomyelitis, epidural abscess, and mycotic aneurysm. High-grade or persistent bacteremia mandates a thorough evaluation for these complications, even if a primary site of infection has been identified. The reported mortality rate for staphylococcal bacteremia ranges from 11 to 43%, with catheter-related infections carrying lower rates of complications and mortality than noncatheter infections.

**Musculoskeletal Infections** *S. aureus* is the most common cause of *acute osteomyelitis* (Chap. 129) in adults and one of the leading causes in children. Acute osteomyelitis develops as a result of either hematogenous seeding of bone (especially damaged bone) or direct extension from a contiguous focus of infection. The most common sites of hematogenous staphylococcal osteomyelitis in adults are the vertebral bodies; in children, the highly vascular metaphyses of long bones are most often affected. Acute osteomyelitis in adults usually presents with constitutional symptoms and pain over the affected area, often developing over several weeks or months. Leukocytosis and an elevated erythrocyte sedimentation rate or C-reactive protein level are laboratory clues to the diagnosis. Bacteremia may or may not be demonstrable. Four weeks of parenteral antibiotic therapy is usually curative.

*S. aureus* is also a prominent cause of *chronic osteomyelitis*, which develops at sites of previous surgery, trauma, or devascularization. In light of the hectic pace of many infections caused by *S. aureus*, chronic staphylococcal osteomyelitis can be impressively indolent; the infection may be asymptomatic for years or even decades, only to reawaken spontaneously and cause pain, sinus tract formation, and purulent drainage. A plain film of the affected area reveals bony destruction. The staphylococcal etiology of infection is best established by biopsy and culture of bone, as cultures of superficial or sinus tract drainage may yield misleading results. Cure requires surgical debridement of necrotic bone followed by a prolonged course of antibiotics.**For consensus definitions of acute and chronic osteomyelitis, see Chap. 129.*

A special form of osteomyelitis is that associated with prosthetic joints or with internal or external fixation devices. Pain, fever, swelling, and decreased range of motion are cardinal features of an infected prosthesis. A plain film may suggest loosening of the prosthesis, often as radiolucency at the interface between bone and cement. *S. aureus* osteomyelitis associated with a prosthesis is infrequently cured by antibiotics alone. Persistent sepsis, persistent bacteremia, and clinical or radiologic evidence of loosening are absolute indications for removal of the prosthesis. *S. aureus* infection of fixation devices requires their removal, although this procedure may occasionally be delayed long enough to allow healing of the underlying fracture. Late relapses after apparent medical cure are not uncommon. A strategy of microbial suppression with oral antibiotics after a course of high-dose parenteral therapy is occasionally employed when removal of hardware is deemed too aggressive a measure for a particular patient.

*S. aureus* is a major cause of *septic arthritis* in adults (Chap. 323). Predisposing factors include injection drug use, rheumatoid arthritis, use of systemic or intraarticular steroids, penetrating trauma, and joints previously damaged by trauma or disease. Knees, hips, and sacroiliac joints are most frequently infected. In addition to parenteral antibiotics, cure requires either repeated joint aspirations -- the end points being sterilization of the joint space, a decrease in the number of leukocytes in the joint aspirate, and no reaccumulation of fluid -- or open or arthroscopic debridement and drainage. Failure to adequately drain joints infected with *S. aureus* poses a risk of permanent loss of function. *S. aureus* is also the most common cause of *septic bursitis* (Chap. 325), which most often involves bursae of the elbows, knees, and shoulders. As in arthritis, adequate drainage (via repeat aspiration, placement of a drain, or open debridement) hastens recovery and minimizes loss of function.

*S. aureus* infection of muscle (*pyomyositis*;Chap. 128) is relatively uncommon in temperate climates; *psoas abscess* is the most common such infection. The psoas muscle is seeded either hematogenously or by direct extension from the site of vertebral osteomyelitis; the results are pain upon extension of the hip and fever. Although formerly a cause of fever of unknown origin, psoas abscess is now relatively easy to diagnose by abdominalCT orMRI. Psoas abscesses are occasionally amenable to drainage via a percutaneous catheter; if not, then surgical drainage is indicated. For reasons that are not well understood, most other cases of staphylococcal pyomyositis occur in the tropics (tropical pyomyositis); in the United States, pyomyositis is seen most often in patients with underlying conditions such as diabetes mellitus, alcoholism, immunosuppressive therapy, and hematologic malignancy.

## DIAGNOSIS

The diagnosis of *S. aureus* infection is generally straightforward and is based on the isolation of the organism either from purulent material or from a normally sterile body fluid. Rarely should *S. aureus* growing from even a single blood culture be considered a contaminant. Clinical samples require no special transport media to preserve the viability of the organisms. Gram's staining of purulent material from a staphylococcal abscess invariably reveals abundant neutrophils and intra- and extracellular gram-positive cocci, which may be found singly or in pairs, tetrads, or clusters. *S. aureus* grows readily on standard laboratory media. Colonies that are catalase-positive

and coagulase- or thermonuclease-positive are identified presumptively as *S. aureus*. Commercial kits are also available for the identification of gram-positive cocci and are generally reliable for identification of *S. aureus*.

The diagnosis of staphylococcal intoxications (such asTSS) may be more difficult and may in fact rely entirely on clinical data. The contribution of the laboratory may be confirmatory -- for example, the demonstration of seroconversion toTSST-1following a compatible illness, the demonstration of toxin production in vitro by a strain isolated from a patient, or the detection ofSE in a food sample.

## TREATMENT

The essential elements of therapy for staphylococcal infections are drainage of purulent collections of pus, debridement of necrotic tissue, removal of foreign bodies, and administration of antimicrobial agents. The importance of adequate drainage cannot be overemphasized; all but the smallest of staphylococcal abscesses require drainage for cure. In skin and soft tissue infections, surgical drainage is occasionally all that is required for cure. It is very difficult to eradicate *S. aureus* infection in the presence of a foreign body, such as a piece of orthopedic hardware, an intravascular catheter or other device, or a pacemaker. For example, patients with catheter-associated bacteremia who are treated with antibiotics but do not have their catheters removed have been found to be six times more likely to experience a relapse or to die of their infection than are patients whose catheters are removed. Only under extraordinary circumstances should an attempt be made to cure such infections without removal of foreign material or debridement of necrotic tissue.

***Antimicrobial Resistance*** The relentless spread of antibiotic resistance among strains of *S. aureus* is one of the great challenges facing clinicians today. Within 4 years of the introduction of penicillin G into clinical practice in 1941,b-lactamase-mediated resistance to penicillin was reported. As additional antibiotics became available in the 1950s, resistance rapidly emerged to them as well. Bacterial killing byb-lactam antibiotics depends on binding of the drugs to penicillin-binding proteins (PBPs), a group of transpeptidases that catalyze the terminal steps in peptidoglycan assembly. *S. aureus* normally produces four PBPs, all of which are inhibited by b-lactam antibiotics and several of which are essential for bacterial integrity and multiplication. Penicillin resistance in *S. aureus* is largely due to bacterial production of b-lactamase, a serine peptidase that enzymatically degrades the b-lactam ring of penicillin, thereby inactivating the drug before it can interact with the PBPs. In most communities,>90% of *S. aureus* strains produce b-lactamase and hence are resistant to penicillin.

Methicillin, the firstb-lactamase-stable semisynthetic penicillin, was introduced in 1960; it took only 1 year, however, for anMRSAstrain to be isolated. Classic methicillin resistance is encoded by the methicillin resistance determinant (*mec*), a 30- to 50-kb transposon-like segment of DNA that is present in MRSA strains and absent from sensitive strains. The *mecA* gene encodes a variantPBPcalled *PBP2¢* or *PBP2a*. PBP2¢ has reduced affinity forb-lactam antibiotics and can substitute for the essential PBPs if they have been inactivated byb-lactams. MRSA strains are resistant to the action of all b-lactam antibiotics, including penicillins, cephalosporins, and carbapenems. Since the early 1980s, these strains have tended to be resistant to most

other antibiotics as well, including chloramphenicol, tetracyclines, and macrolides, through other resistance mechanisms. Nosocomial (as opposed to community-acquired) isolates of MRSA are especially likely to be multidrug-resistant. Classic methicillin resistance can be detected readily in the clinical microbiology laboratory by a variety of techniques. An additional mechanism of relative resistance to methicillin -- hyperproduction ofb-lactamase -- has been described, but the clinical significance of this form of resistance is uncertain.

Until recently, all strains ofMRSAremained susceptible to vancomycin (if nothing else), making this the drug of choice for the treatment of infections caused by suspected or proven MRSA. Unfortunately, the efficacy of vancomycin for serious *S. aureus* infections, regardless of susceptibility to other agents, is suboptimal (see "Selection of Antibiotics," below). Furthermore, resistance of *S. aureus* to vancomycin has now emerged as well (see below), making the search for new antistaphylococcal agents all the more urgent. If isolates are shown to be susceptible to clindamycin or trimethoprim-sulfamethoxazole, these agents can be effective for treatment of MRSA infection -- but again, many strains are resistant. Two newly licensed antibiotics, representing the vanguard of two new classes of drugs, may prove to be useful for treatment of infections caused by MRSA. A new antibiotic that combines two streptogramins, quinupristin and dalfopristin, blocks protein synthesis at two ribosomal sites, resulting in a synergistic bactericidal effect on *S. aureus* and other gram-positive cocci. Linezolid, the first representative of the new oxazolidinone class of antibiotics, also demonstrates excellent activity against *S. aureus*, including multidrug-resistant strains of MRSA. Oxazolidinones are bacteriostatic, but resistance to them is unusual and there is no cross-resistance with other classes of compounds. Until data reveal the relative efficacies and toxicities of vancomycin and these new compounds, however, vancomycin remains the drug of choice for treatment of MRSA infections.

In 1996, a long-predicted monster -- *S. aureus* with decreased susceptibility to vancomycin -- finally emerged from the theoretical nightmares of microbiologists into the clinical realm. The term *vancomycin-intermediate S. aureus* (VISA) has been widely used to describe these strains, whose minimum inhibitory concentrations (MICs) of vancomycin (8 to 16 ug/mL) should theoretically confer only intermediate resistance to this agent. The clinical experience has been one of treatment failure, however. In 1997, four patients with VISA infection were reported from Japan and the United States; all died, although only one death was a direct result of the VISA infection. As of this writing, about a dozen additional cases have been reported from Asia, North America, and Europe, and the VISA genotype is already widespread in Japan. The risk factors for infection with VISA are uncertain because of the small number of reported cases, but they appear to include a history of dialysis, multiple prior courses of antibiotics (including vancomycin), admission to an intensive care unit, and prior infection withMRSA.

The mechanism for decreased susceptibility to vancomycin in *S. aureus* appears to be novel and unrelated to the mechanism of resistance of vancomycin-resistant enterococci (VRE).VISAstrains have unusually thick extracellular matrices that make it more difficult for vancomycin to reach its binding site at the level of the murein monomer of the cell wall. In addition, peptidoglycan from VISA appears to bind more vancomycin than does peptidoglycan from susceptible strains of *S. aureus*. These two factors create a "vancomycin sink," resulting in an increase in theMIC of vancomycin. VISA strains

may also be characterized by increased expression ofPBPs, slower growth, and decreased autolysis, all potentially contributing to antimicrobial resistance. Vancomycin resistance within a population of organisms is expressed in a heterogeneous manner, which may lead to difficulty in detection of the phenotype by usual susceptibility testing and may explain the failure of antimicrobial therapy in some cases. Therefore, infection with VISA should be suspected in any patient for whom seemingly appropriate therapy with vancomycin is ineffective. Removal of prosthetic material associated with infection is even more critical than usual in treating a patient infected withMRSA or VISA. Antimicrobial therapy for infections caused by VISA is discussed below (see "Selection of antibiotics").

In recent years, the percentage of staphylococcal isolates that are methicillin-resistant has risen substantially in U.S. hospitals; this trend has been driven by widespread (and often indiscriminate) antibiotic use. In some tertiary care institutions, up to 40% of *S. aureus* isolates are now resistant to methicillin, although rates of 5 to 15% are more typical. This situation is problematic for several reasons. Hospitalized patients colonized withMRSA are at increased risk (up to fourfold higher) of developing staphylococcal bacteremia than are patients colonized with methicillin-sensitive strains. The extent to which this difference reflects differences in bacterial virulence (as opposed to host factors or appropriateness of therapy) remains unclear; MRSA strains have not been shown consistently to be more virulent than sensitive strains, but the breadth of their resistance renders colonization more persistent, which in turn increases the rate of infection. In addition, higher rates of MRSA infection within an institution cause increased use of vancomycin, which contributes to the emergence ofVRE and apparently puts additional pressure on MRSA to develop resistance to vancomycin as well.

A second development over the past decade has been an apparent increase in the incidence in some communities ofMRSAinfection among individuals without apparent risk factors for MRSA. Previously identified risk factors for MRSA include residence in a long-term-care facility; hospitalization; chronic liver, lung, or vascular disease; dialysis; malignancy; and prolonged exposure to antibiotics. An increase in community-acquired cases of MRSA infection has been reported in several locations in the United States and suggests a change in the epidemiology of infection with this organism. It is hypothesized that strains of MRSA spread from the hospital to the community, where continued exposure to antibiotics (both appropriate and unnecessary) leads to their survival advantage and persistence. These reports have been based on retrospective observations, however, and have not yet been confirmed by prospective studies. The obvious question is whetherb-lactam antibiotics should continue to be used as the empirical agents of choice for community-acquired staphylococcal infections. For the time being, the incidence of MRSA infection in the community seems too low to justify more widespread use of vancomycin in this setting. There are situations, however, in which empirical use of vancomycin for community-acquired infections is justifiable and even advisable, as discussed below.

***Selection of Antibiotics (Table 139-2)*** Although most pathogenic strains of *S. aureus* are resistant to penicillin, the development of penicillins and cephalosporins that are resistant tob-lactamase has allowed these classes of antibiotics to remain useful for treatment of most *S. aureus* infections. Nafcillin and oxacillin, both of which are

b-lactamase-resistant penicillins, are the drugs of choice for parenteral treatment of serious staphylococcal infections. Penicillin remains the drug of choice for infections caused by susceptible organisms. Drug combinations consisting of a penicillin plus a b-lactamase inhibitor are also effective but are best reserved for treatment of polymicrobial infections. Penicillin-allergic patients can usually be given a cephalosporin, although caution should be exercised if the prior adverse reaction to penicillin was anaphylaxis. Of the cephalosporins, the first-generation agents (e.g., cefazolin) are preferred for reasons related to cost and breadth of spectrum. For patients who are intolerant of all b-lactam agents, the best alternatives for parenteral administration are vancomycin and clindamycin. Dicloxacillin and cephalexin are recommended for oral treatment of minor infections or for continuation therapy; clindamycin is an alternative oral agent for most strains. Routine use of quinolones is not recommended because of the possibility of emergent resistance during therapy.

Use of vancomycin has increased dramatically over the past 20 years in response to the emergence ofMRSA, for which it has often been the sole therapeutic option, and the increasing number of infections caused byCoNS and other gram-positive cocci. Vancomycin's favorable pharmacokinetic properties and relatively low toxicity profile have also contributed to its widespread use. Unfortunately, increased use of vancomycin has resulted in the emergence of bothVRE andVISA, which are now poised to be the microbial scourges of the next decade. Equally important, however, is the fact -- often not recognized by practitioners -- that vancomycin is *less effective* than numerous other agents at our disposal. Vancomycin is generally only weakly bactericidal or even bacteriostatic for many strains of *S. aureus*. Studies of animal models have repeatedly shown vancomycin to be inferior to b-lactam agents for treatment of serious staphylococcal infections. Bacteremia is cleared more slowly in patients treated with vancomycin than in those treated withb-lactams, and clinical cure rates with vancomycin are significantly lower than with b-lactams as well. For all of these reasons, use of vancomycin should be reserved for situations in which there are no suitable alternative agents. It should not be used routinely for prophylaxis of staphylococcal infections, for empirical therapy in patients with fever and neutropenia (unless staphylococcal infection is especially likely), for decontamination of the digestive tract, for clearance of MRSA colonization, or for treatment of established gram-positive infections not due to resistant organisms. It is hoped that judicious use of vancomycin will help limit the spread of VRE and VISA and ensure that patients receive the most potent therapeutic agents.

Vancomycin remains the drug of choice for treatment of infections caused byMRSA, although sensitive strains may be amenable to therapy with clindamycin or trimethoprim-sulfamethoxazole. As discussed above, two new agents, quinupristin/dalfopristin and linezolid, offer promise for treatment of MRSA, but further studies are needed before they can be recommended for routine or preferential use. Optimal therapy for infections caused byVISA is unknown. To date, all isolates of VISA have been susceptible to alternative agents. Therapeutic options include the combination of vancomycin plus ab-lactam (based largely on in vitro data), quinupristin/dalfopristin, linezolid, or one of the new quinolone antibiotics, although the potential for development of resistance to the quinolones during therapy makes their use a questionable approach for infections requiring a prolonged course of antibiotic.

In most clinical settings, no significant benefit is attained by treating *S. aureus* infections with more than one drug to which the organism is known to be susceptible. Synergy has been demonstrated in vitro forb-lactam/aminoglycoside combinations, which hasten sterilization of the blood in endocarditis. Accordingly, therapy for *S. aureus* bacteremia is often initiated with such a combination for a brief period (e.g., 5 to 7 days) -- a strategy that seems reasonable when rapid clearance of bacteremia is deemed to be critical, as in prosthetic valve endocarditis. Thereafter, the toxicity of an aminoglycoside cannot be justified. Use of rifampin in conjunction with ab-lactam antibiotic (or vancomycin) occasionally results in microbial eradication and clinical cure of otherwise refractory infections, particularly those involving foreign bodies that are judged to be unremovable or those involving avascular tissue. These successes may relate to the high level of activity of rifampin against intracellular organisms, includingSCVs. Chronic osteomyelitis, parameningeal infections, and septic phlebitis have all been successfully treated with rifampin plus a cell wall-active agent. Nevertheless, routine use of rifampin for serious *S. aureus* infections is not recommended because of potential added toxicity, drug interactions, and theoretical antimicrobial antagonism. Rifampin should be reserved for refractory, relapsing, or inoperable infections and should never be administered as monotherapy, which rapidly leads to resistance.

***Route and Duration of Therapy*** Because of poor bioavailability of most oral antistaphylococcal agents, parenteral therapy should be used for infections that require high concentrations of antibiotic, such as endovascular infections, infections of poorly vascularized tissue (including abscesses), and infections of the central nervous system. Given the propensity of *S. aureus* to adhere to endovascular and devitalized or damaged tissues, high doses of antibiotics (e.g., 12 g/d of nafcillin) should be used for bacteremic infections. When high serum levels of antibiotic are required to produce adequate tissue levels (e.g., in endocarditis or osteomyelitis), the parenteral route should be used for the duration of therapy. Oral agents may suffice for the treatment of nonbacteremic infections in which high serum levels of antibiotic are not requisite (e.g., skin, soft tissue, and upper respiratory tract infections).

With the notable exceptions of bacteremia (including endocarditis) and osteomyelitis, the duration of therapy for *S. aureus* infections can be tailored to the severity of illness, the immunologic status of the host, and the response to treatment. Because antibiotics penetrate bone poorly, treatment of acute osteomyelitis in adults requires at least 4 weeks of parenteral therapy. Chronic osteomyelitis is often treated with 6 to 8 weeks of parenterally administered antibiotics followed by several months of oral therapy, especially if the adequacy of debridement is uncertain.

Acute endocarditis and other endovascular infections caused by *S. aureus* should be treated with parenteral antibiotics for 4 weeks (6 weeks in the case of prosthetic valves). Simple bacteremia, as might occur with a removable or drainable focus of infection, is curable with a shorter duration of therapy, but a 2-week course of *parenteral* therapy has traditionally been recommended *for all patients* with *S. aureus* bacteremia, even under these circumstances. The costs and effort implicit in this recommendation are apparent, but shorter courses of therapy are associated with an unacceptable rate of secondary complications. Data suggest that a 7-day course of parenteral therapy may be adequate for simple bacteremia if the clinical response to therapy is prompt, if cultures of blood obtained after 2 days of therapy are negative, and ifTEE is negative for

vegetations. These data require confirmation, however. One of the more challenging aspects of treating staphylococcal bacteremia is deciding whether to administer parenteral therapy for 2 or 4 weeks. A conservative approach (one that is supported by numerous studies) dictates that *4 weeks* should be standard unless specific criteria are met (Fig. 139-2).

## PREVENTION AND CONTROL

Nosocomial staphylococcal outbreaks and the spread of resistant strains of *S. aureus* are serious global problems. Within an institution, the most important vector of transmission of *S. aureus* is the hands of health care workers. Patients with exposed wounds or with nasal colonization are important reservoirs of the organisms. Transmission of *S. aureus* -- and hence the incidence of staphylococcal infection within an institution -- can be reduced most effectively by meticulous hand washing before and after contact with patients. The incidence of postoperative staphylococcal infection can be reduced by perioperative administration of an antibiotic with a favorable spectrum of activity and favorable pharmacokinetic properties, such as cefazolin, cefuroxime, or vancomycin. Elimination of nasal carriage before surgery (see below) may also prove to be effective in this regard.

More stringent infection-control measures must be taken to prevent the nosocomial spread ofMRSA. Such measures include assigning patients colonized or infected with MRSA to private rooms, wearing gloves for contact with contaminated wounds and mucous membranes as well as a gown if contamination of clothing is likely, and hand washing with an antiseptic soap after patient contact. Patients who are colonized but not infected with MRSA should not be treated with vancomycin merely for the sake of eliminating carriage of this organism.

Staphylococcal skin and soft tissue infections may recur once a person has been colonized with a virulent strain. In this context, therapy directed at the elimination of staphylococcal colonization may be warranted, especially for patients at particular risk for complications of infection. Use of an oral b-lactam antibiotic alone is ineffective, but combination therapy for 10 to 14 days with dicloxacillin or cephalexin (500 mg four times a day) plus rifampin (300 mg twice a day) plus mupirocin (2% ointment applied topically to both nares twice a day) is usually effective at clearing the carrier state, at least for a period of months.

## COAGULASE-NEGATIVE STAPHYLOCOCCI

CoNSare a major cause of nosocomial infection and are the organisms most frequently isolated from the blood of hospitalized patients. The frequency with which they cause opportunistic infection in immunocompromised hosts attests more to the increased vulnerability of such hosts in modern medical practice than to the intrinsic virulence of the organisms. Despite the weak pathogenicity of these bacteria, the global impact of CoNS infection is considerable, including increased length and cost of hospital stay; increased use of antibiotics in general; and increased use of vancomycin in particular, which has contributed to the recent emergence of vancomycin-resistant gram-positive bacteria.

Although the variety of clinical syndromes caused byCoNS is impressive, several characteristics apply to most such infections. First, they tend to be *indolent*. There is often a long latent period between the time of contamination (e.g., of a medical device) and the onset of clinical illness; bacteremia in neutropenic patients can be an exception to this rule. Second, most CoNS infections are nosocomial in origin; important exceptions are prosthetic valve endocarditis and *S. saprophyticus* infections of the urinary tract. Third, most clinically significant infections are caused by strains of CoNS that are resistant to multiple antibiotics, including penicillins and cephalosporins. Finally, most CoNS infections are associated with a medical device of some kind, and removal of such devices is often required for cure.

## EPIDEMIOLOGY AND PATHOGENESIS

CoNS, particularly *S. epidermidis*, are invariable and prominent constituents of the normal human skin flora. Infection most often results from direct inoculation of a foreign body at the time it is inserted, although hematogenous seeding can also occur.

CoNSare the quintessential pathogens of medical devices. The array of virulence factors produced by CoNS is meager compared with that of the virulence factors produced by *S. aureus*, but among these few factors are substances that promote bacterial adherence to and persistence on foreign bodies. A variety of surface antigens that promote colonization of medical devices by CoNS (particularly *S. epidermidis*) have been proposed; the best-studied of these is capsular polysaccharide adhesin, which serves as the organism's capsule and promotes the initial interaction of the bacteria and a foreign body. This polysaccharide is a major component of the *S. epidermidis* biofilm, which is important in the persistence of infection; the biofilm thwarts host defenses by coating staphylococcal cells onto foreign materials and impairing phagocytic killing. CoNS appear not to make toxic exoproteins or toxins; rather, they cause disease by tenaciously persisting on foreign materials, resulting in a local and occasionally a systemic inflammatory response.

The most important risk factor for infection withCoNS is the presence of a foreign body, especially an indwelling catheter. A second major risk factor for infection is deficient phagocyte function -- especially neutropenia, which is most often an iatrogenic complication of chemotherapy for cancer but may also reflect an underlying disease process (such as leukemia). The likelihood of catheter-related infection depends upon a number of variables, including the experience and skill of the person who inserts the catheter, the length of time that a catheter is left in place, and the quality of postinsertion care of the catheter site. CoNS only rarely cause infections (other than urinary tract infections) in immunologically normal hosts and typically do so only under extenuating circumstances.

## CLINICAL SYNDROMES

BecauseCoNS can adhere to a variety of materials, virtually all *foreign bodies* are susceptible to colonization by these organisms. CoNS are the most common pathogens complicating the use of intravenous catheters, hemodialysis shunts and grafts, cerebrospinal fluid (CSF) shunts, peritoneal dialysis catheters, pacemaker wires and electrodes, prosthetic joints, vascular grafts, and prosthetic valves. CoNS infection of

intravenous catheters may or may not be accompanied by signs of inflammation at the site of catheter insertion, and the degree of systemic toxicity (including fever) ranges from minimal to moderately severe. The diagnosis can be established by the culturing of blood drawn from the catheter and by venipuncture. Infection of CSF shunts is usually evident within several weeks of implantation. Signs of meningitis are sometimes readily apparent but more often are subtle or absent; malfunction of the shunt may be the only manifestation of shunt infection. CoNS infection of a prosthetic joint often does not become evident until long after implantation, although the inciting contamination usually occurs at the time of implantation. Infection of vascular grafts may result in the development of an aneurysm or a pseudoaneurysm, with catastrophic consequences.

CoNSare a prominent cause of *bacteremia* in immunosuppressed patients. While such infections in immunocompetent hosts are relatively benign, patients with neutropenia may have high-grade bacteremia that results in significant systemic toxicity. A serious consequence of bacteremia is the seeding of a secondary foreign body, such as a prosthetic heart valve or joint or a pacemaker.

CoNSare the organisms most commonly responsible for *prosthetic valve endocarditis*, causing the majority of infections that develop within several months of implantation as well as a substantial percentage of late infections. The syndrome is one of subacute endocarditis (thus contrasting with the syndrome produced by *S. aureus*), with an illness that is clinically indistinguishable from that caused by viridans streptococci. Infection of prosthetic valves is often complicated by valvular dysfunction secondary either to dehiscence of the sewing ring or obstruction of the valve's orifice by bulky vegetations. CoNS are a less frequent but important cause of *native valve endocarditis*, accounting for<5% of such infections and usually affecting abnormal valves.

*S. saprophyticus* is a common cause of *urinary tract infection* among sexually active young women, in whom it is second only to *E. coli* in frequency. Exposure to spermicide-coated condoms may increase the incidence of infection. *S. saprophyticus* produces a syndrome indistinguishable from that caused by other etiologic agents, with pyuria and symptoms of dysuria, frequency, and abdominal pain. Infection with *S. saprophyticus* is readily amenable to therapy with most agents commonly used to treat urinary tract infections.CoNS can also cause urinary tract infection in hospitalized patients who have undergone invasive procedures; such infections are especially likely to be asymptomatic and may be difficult to treat because of antimicrobial resistance.

**DIAGNOSIS**

AlthoughCoNS are the most common cause of nosocomial bacteremia, they are also the most common contaminants of blood cultures; differentiation between infection and contamination often poses a challenge, with major therapeutic implications. Positive blood cultures are more likely to be "true positives" when there is a clinical illness suggestive of infection, when there is an indwelling catheter or some other risk factor for CoNS infection, and when cultures of blood drawn from multiple sites are positive for phenotypically identical organisms with the same antimicrobial susceptibility patterns. Except in the setting of neutropenia, physicians often have the luxury of awaiting the results of repeat cultures when the significance of CoNS growing from a blood culture is questionable.

## TREATMENT

Removal of the foreign body (especially when it is an intravenous catheter) often constitutes adequate therapy forCoNSinfection related to that device. Most infections involving a foreign body require the removal of the device -- whether a prosthetic valve, prosthetic joint,CSFshunt, vascular graft, pacemaker or defibrillator and associated hardware, or hemodialysis shunt. Cures of all such infections with antibiotics alone have been reported, however, and a patient's poor medical condition or the hazards of surgery occasionally warrant an attempt at medical cure without extirpation of the device (see below). Infections of peritoneal dialysis catheters can be cured with antibiotics alone often enough that an attempt should be made to do so. CoNS infections of central venous catheters are also amenable to medical therapy, although relapses are common. Persistent bacteremia during therapy is an absolute indication for removal of a catheter, and bacteremia after a catheter's removal suggests seeding of a secondary site.

It is difficult to make generalizations about the optimal duration of therapy forCoNSinfections. In general, the duration of treatment is the same as for infection syndromes caused by other bacteria. For example, native valve endocarditis should be treated for 4 weeks, prosthetic valve endocarditis for 6. Transient bacteremia in an immunocompetent host may require no antimicrobial therapy after removal of an offending catheter. The efficacy of therapy can occasionally be enhanced by the delivery of antibiotics directly to the site of infection -- e.g., by intraventricular administration of vancomycin for central nervous system infections or by intraperitoneal administration of antibiotic for infections of peritoneal dialysis catheters.

Despite the low degree of pathogenicity ofCoNS, treatment of serious infections due to these organisms is often problematic because of the high percentage of strains that are resistant to commonly used antibiotics, including most oral agents. Most strains of CoNS isolated from patients in U.S. hospitals are resistant not only to penicillin but also to the penicillinase-resistant penicillins and cephalosporins. Nosocomial isolates are usually resistant to other classes of antibiotics as well. Vancomycin, to which the vast majority of CoNS remain susceptible, is of necessity the drug of choice for *empirical* therapy for serious CoNS infections. Strains proved to be susceptible to nafcillin (oxacillin) or penicillin should be treated with one of these agents or with a first-generation cephalosporin.

Synergistic combinations of antibiotics are often useful in the treatment ofCoNSinfections. Rifampin plays a unique role in this endeavor by virtue of its potency against most staphylococci, its excellent penetration into tissues (including those that are poorly vascularized), and the high levels it reaches within human cells and biofilm. Rifampin must be used in combination with other antibiotics because of the frequent and rapid emergence of microbial resistance to the drug when it is used alone. If an effort must be made to eradicate infection of a medical device without its removal, the concomitant use of ab-lactam antibiotic to which the organism is susceptible plus rifampin (300 mg twice daily by mouth) plus gentamicin affords the best chance for success. Vancomycin can be substituted for theb-lactam agent if so dictated by an organism's susceptibility pattern or by a patient's drug allergy.

(Bibliography omitted in Palm version)

Back to Table of Contents

## 140. STREPTOCOCCAL AND ENTEROCOCCAL INFECTIONS - *Michael R. Wessels*

Many varieties of streptococci are found as part of the normal human flora colonizing the respiratory, gastrointestinal, and genitourinary tracts. Several species are important causes of human disease. Group A *Streptococcus*, or *S. pyogenes*, is responsible for streptococcal pharyngitis, one of the most common bacterial infections of school-age children, and for the postinfectious syndromes of acute rheumatic fever and poststreptococcal glomerulonephritis. Group B *Streptococcus*, or *S. agalactiae*, is the leading cause of bacterial sepsis and meningitis in newborns and a major cause of endometritis and fever in parturient women. Enterococci are important causes of urinary tract infection, nosocomial bacteremia, and endocarditis. Viridans streptococci are the most common cause of bacterial endocarditis.

Streptococci are gram-positive bacteria of spherical to ovoid shape that characteristically form chains when grown in liquid media. Most streptococci that cause human infections are facultative anaerobes, although some are strict anaerobes. Streptococci are relatively fastidious organisms, requiring enriched media for growth in the laboratory. No single scheme for classification of streptococci is entirely satisfactory. Consequently, clinicians and clinical microbiologists often identify streptococci by any of several classification systems, including hemolytic pattern, Lancefield group, species name, and common or trivial name. Many of the streptococci associated with human infection produce a zone of complete hemolysis around the bacterial colony when cultured on blood agar, a pattern known as *b hemolysis*. Theb-hemolytic streptococci can be classified by the Lancefield system, a serologic grouping based on the reaction of specific antisera with cell-wall carbohydrate antigens of the bacteria. With rare exceptions, organisms belonging to Lancefield groups A, B, C, and G are allb-hemolytic streptococci, and each is associated with characteristic patterns of human infection. Other streptococci produce a zone of partial (a) hemolysis, often imparting a greenish appearance to the agar. These a-hemolytic streptococci are further identified by biochemical testing and include *S. pneumoniae*, an important cause of pneumonia, meningitis, and other infections, and several species of streptococci referred to collectively as the *viridans streptococci*, which are part of the normal oral flora and are important as agents of subacute bacterial endocarditis. Finally, some streptococci are nonhemolytic, a pattern sometimes called *ghemolysis*. The classification of the major groups of streptococci responsible for human infections is outlined inTable 140-1. Among the organisms classified serologically as group D streptococci, the enterococci are now considered to constitute a separate genus on the basis of DNA homology studies. Thus, species previously designated as *S. faecalis* and *S. faecium* have been renamed *Enterococcus faecalis* and *E. faecium*, respectively.**For further discussion of pneumococcal infections, see Chap. 138.*

### GROUP A STREPTOCOCCI

Lancefield's group A consists of a single species, *S. pyogenes*. As its species name implies, this organism is associated with a variety of suppurative infections. In addition, group A streptococci can trigger the postinfectious syndromes of acute rheumatic fever (which is uniquely associated with *S. pyogenes* infection;Chap. 235) and poststreptococcal glomerulonephritis (Chap. 274).

## PATHOGENESIS

Group A streptococci elaborate a number of cell-surface components and extracellular products important both in the pathogenesis of infection and in the immune response of the human host. The cell wall contains a carbohydrate antigen that may be released by treatment with acid. The reaction of such acid extracts with group A-specific antiserum is the basis for the definitive identification of a streptococcal strain as *S. pyogenes*. The major surface protein of group A streptococci is M protein, which occurs in more than 100 antigenically distinct types and is the basis for the serotyping of strains with specific antisera. The M protein molecules are fibrillar structures anchored in the cell wall of the organism and extending as hairlike projections away from the cell surface. The amino acid sequence of the distal or amino-terminal portion of the M protein molecule is quite variable, accounting for the antigenic variation of the different M types, while more proximal regions of the protein are relatively conserved. A newer technique for assignment of M type to group A streptococcal isolates uses the polymerase chain reaction to amplify the variable region of the M protein gene. DNA sequence analysis of the amplified gene segment can be compared with an extensive data base [developed at the Centers for Disease Control and Prevention (CDC)] for assignment of M type. This method eliminates the need for typing sera, which are available in only a few reference laboratories. The presence of M protein on a group A streptococcal isolate correlates with its capacity to resist phagocytic killing in fresh human blood; this phenomenon appears to be due, at least in part, to the binding of plasma fibrinogen to M protein molecules on the streptococcal surface, which interferes with complement activation and deposition of opsonic complement fragments on the bacterial cell. This resistance to phagocytosis may be overcome by M protein-specific antibodies, and thus individuals with antibodies to a given M type acquired as a result of prior infection are protected against subsequent infection with organisms of the same M type but not against that with different M types.

Group A streptococci also elaborate, to varying degrees, a polysaccharide capsule composed of hyaluronic acid. The production of large amounts of hyaluronic acid capsule by certain strains lends a characteristic mucoid appearance to the bacterial colonies. The capsular polysaccharide also plays an important role in protecting the organisms from ingestion and killing by phagocytes. In contrast to M protein, the hyaluronic acid capsule is a weak immunogen, and antibodies to hyaluronate have not been shown to be important in protective immunity; the presumed explanation is the apparent structural identity between streptococcal hyaluronic acid and the hyaluronic acid of mammalian connective tissues. The capsular polysaccharide may also play a role in group A streptococcal colonization of the pharynx by binding to CD44, a hyaluronic acid-binding protein expressed on human pharyngeal epithelial cells.

Group A streptococci produce a large number of extracellular products that may be important in local and systemic toxicity and in the spread of infection through tissues. These products include streptolysins S and O, toxins that damage cell membranes and account for the hemolysis produced by the organisms; streptokinase; DNases; protease; and pyrogenic exotoxins A, B, and C. The pyrogenic exotoxins, previously known as erythrogenic toxins, cause the rash of scarlet fever. Since the mid-1980s, pyrogenic exotoxin-producing strains of group A *Streptococcus* have been linked to unusually severe invasive infections, including necrotizing fasciitis and a systemic syndrome

termed the *streptococcal toxic shock syndrome*. Several extracellular products stimulate specific antibody responses useful in the serodiagnosis of recent streptococcal infection. Tests for these antibodies are used primarily for the detection of preceding streptococcal infection in cases of suspected acute rheumatic fever or poststreptococcal glomerulonephritis.

## CLINICAL MANIFESTATIONS

**Pharyngitis** Although seen in patients of all ages, group A streptococcal pharyngitis is one of the most common bacterial infections of childhood, accounting for 20 to 40% of all cases of exudative pharyngitis in children. It is rare among those under the age of 3. Younger children may manifest streptococcal infection with a syndrome of fever, malaise, and lymphadenopathy without exudative pharyngitis. Infection is acquired through contact with another individual carrying the organism. Respiratory droplets are the usual mechanism of spread, although other routes, including food-borne outbreaks, have been well described.

The incubation period is 1 to 4 days. Symptoms include sore throat, fever and chills, malaise, and sometimes abdominal complaints and vomiting, particularly in children. Both symptoms and signs are quite variable, ranging from mild throat discomfort with minimal physical findings to high fever and severe sore throat associated with intense erythema and swelling of the pharyngeal mucosa and the presence of purulent exudate over the posterior pharyngeal wall and tonsillar pillars. Enlarged, tender anterior cervical lymph nodes commonly accompany exudative pharyngitis.

The differential diagnosis of streptococcal pharyngitis includes the many other bacterial and viral causes of pharyngitis. Streptococcal infection is unlikely to be the cause of pharyngitis when symptoms and signs suggestive of viral infection are prominent (conjunctivitis, coryza, cough, hoarseness, or discrete ulcerative lesions of the buccal or pharyngeal mucosa). Other infections commonly producing exudative pharyngitis include infectious mononucleosis and adenovirus infection. Now rare in the United States, the pseudomembrane of diphtheria may give a similar appearance. The coryneform organism *Arcanobacterium haemolyticum* may cause pharyngitis, often in association with a scarlet fever-like rash (Chap. 141). Other causes of pharyngitis, usually without a purulent exudate, include coxsackievirus, influenza virus, mycoplasmas, and *Neisseria gonorrhoeae* and acute infection with HIV. Because of the range of clinical presentations of streptococcal pharyngitis and the large number of other agents that can produce the same clinical picture, diagnosis of streptococcal pharyngitis on clinical grounds alone is not reliable.

The throat culture remains the diagnostic "gold standard." Culture of a throat specimen that is properly collected (i.e., by vigorous rubbing of a sterile swab over both tonsillar pillars) and properly processed is the most sensitive and specific means available to make a definitive diagnosis. A rapid diagnostic kit using latex agglutination or enzyme immunoassay of swab specimens can serve as a useful adjunct to the throat culture. While precise figures on sensitivity and specificity vary among studies, the rapid diagnostic kits generally are>95% specific. Thus a positive result can be relied upon for definitive diagnosis and eliminates the need for a throat culture. However, because the rapid diagnostic tests are less sensitive than throat culture (with a relative sensitivity

ranging from 55 to 90% in comparative studies), a negative result should be confirmed with a throat culture.

**TREATMENT**

In the usual course of uncomplicated streptococcal pharyngitis, symptoms resolve after 3 to 5 days. The course is shortened little by treatment, which is given primarily to prevent suppurative complications and rheumatic fever. Prevention of rheumatic fever depends on eradication of the organism from the pharynx, not simply on resolution of symptoms, and requires 10 days of penicillin treatment -- either a single intramuscular dose of benzathine penicillin G or a 10-day course of oral penicillin (Table 140-2). Erythromycin may be substituted for penicillin in the treatment of individuals allergic to penicillin. Follow-up culture after treatment is no longer routinely recommended but may be warranted in selected cases, such as those involving patients or families with frequent streptococcal infections or those occurring in situations in which the risk of rheumatic fever is thought to be high (e.g., when cases of rheumatic fever have recently been reported in the community).

*Complications* Suppurative complications of streptococcal pharyngitis have become uncommon with the widespread use of antibiotics for most cases of symptomatic streptococcal infection. The complications result from the spread of infection from the pharyngeal mucosa to deeper tissues by direct extension or by the hematogenous or lymphatic route and may include cervical lymphadenitis, peritonsillar or retropharyngeal abscess, sinusitis, otitis media, meningitis, bacteremia, endocarditis, and pneumonia. Local complications, such as abscess formation in the peritonsillar or parapharyngeal space, should be considered in a patient with unusually severe or prolonged symptoms or localized pain associated with high fever and a toxic appearance.

**Asymptomatic Carrier State** Surveillance cultures have shown that up to 20% of individuals in certain populations may have asymptomatic pharyngeal colonization with group A streptococci. There are no definitive guidelines for management of these asymptomatic carriers or of asymptomatic individuals who still have a positive throat culture after a full course of treatment for symptomatic pharyngitis. A reasonable course of action is to give a single 10-day course of penicillin for symptomatic pharyngitis and, if positive cultures persist, not to re-treat unless symptoms recur. Studies of the natural history of streptococcal carriage and infection have shown that the risk both of developing rheumatic fever and of transmitting infection to others is substantially lower among asymptomatic carriers than among individuals with symptomatic pharyngitis. Therefore, overly aggressive attempts to eradicate carriage are probably not justified under most circumstances. An exception is the situation in which an asymptomatic carrier is a potential source of infection to others. Outbreaks of food-borne infection and nosocomial puerperal infection have been traced to asymptomatic carriers who may harbor the organisms in the throat, on the skin, or in the vagina or anus.

**TREATMENT**

In cases in which a carrier is transmitting infection to others, attempts to eradicate carriage are warranted, although data are limited on the best regimen to use to clear the organism after penicillin alone has failed. The combination of penicillin V (500 mg four

times daily for 10 days) and rifampin (600 mg twice daily for the last 4 days) has been used to eliminate pharyngeal carriage. A 10-day course of oral vancomycin (250 mg four times daily) and rifampin (600 mg twice daily) has eradicated rectal colonization. However, experience is not extensive with any regimen.

**Scarlet Fever** Scarlet fever consists of streptococcal infection, usually pharyngitis, accompanied by a characteristic rash. The rash arises from the effects of one of three toxins, currently designated streptococcal pyrogenic exotoxins A, B, and C and previously known as erythrogenic or scarlet fever toxins. In the past, scarlet fever was thought to reflect infection of an individual lacking toxin-specific immunity with a toxin-producing strain of group A *Streptococcus*. Susceptibility to scarlet fever was correlated with results of the Dick test. A small amount of erythrogenic toxin injected intradermally produced local erythema in susceptible individuals but elicited no reaction in those with specific immunity. Subsequent studies have suggested that development of the scarlet fever rash may reflect a hypersensitivity reaction requiring prior exposure to the toxin. For reasons that are not clear, scarlet fever has become less common in recent years, although strains of group A streptococci that produce pyrogenic exotoxins continue to be prevalent in the population.

The symptoms of scarlet fever are the same as those of pharyngitis alone (Fig. 140-CD1). The (Fig. 140-CD2) rash typically begins on the first or second day of illness over the upper trunk, spreading to involve the extremities but sparing the palms and soles. The rash is made up of minute papules, giving a characteristic "sandpaper" feel to the skin. Associated findings include circumoral pallor, "strawberry tongue" (Fig. 140-CD3) (enlarged papillae on a coated tongue, which later may become denuded), and accentuation of the rash in the skin folds (Pastia's lines). Subsidence of the rash in 6 to 9 days is followed after several days by desquamation of the palms and soles. The differential diagnosis of scarlet fever includes other causes of fever and generalized rash, such as measles and other viral exanthems, Kawasaki disease, toxic shock syndrome, and systemic allergic reactions (e.g., drug eruptions).

**Skin and Soft Tissue Infections** Group A streptococci -- and occasionally other streptococcal species -- cause a variety of infections involving the skin (Fig. 140-CD4), subcutaneous tissues, muscles, and fascia (Fig. 140-CD5). While several clinical syndromes, recognized according to the tissues involved, offer a useful means for classification of skin and soft tissue infections, not all cases fit exactly into a single category. The classic syndromes should be considered as general guides to predicting the level of tissue involvement in a particular patient, the probable clinical course, and the likelihood that surgical intervention or aggressive life-support will be required.

*Impetigo (Pyoderma)* Impetigo is a superficial infection of the skin caused primarily by group A streptococci and occasionally by other streptococci or by *Staphylococcus aureus*. Impetigo is seen most often in young children, tends to occur during the warmer months, and is more common in semitropical or tropical climates than in cooler regions. Infection is more common among children living under conditions of poor hygiene. Prospective studies have shown that colonization of unbroken skin with group A streptococci precedes the development of clinical infection. Minor trauma, such as a scratch or an insect bite, may then serve to inoculate organisms into the skin. Impetigo is best prevented, therefore, by attention to adequate hygiene. The usual sites of

involvement are the face (particularly around the nose and mouth) and the legs, although lesions may occur at other locations. Individual lesions begin as red papules, which evolve quickly into vesicular and then pustular lesions that break down and coalesce to form characteristic honeycomb-like crusts (Plate IID-38). Lesions are generally not painful, and patients do not appear ill. Fever is not a feature of impetigo and, if present, suggests either infection extending to deeper tissues or another diagnosis.

The classic presentation of impetigo usually poses little diagnostic difficulty. Cultures of impetiginous lesions often yield *S. aureus* as well as group A streptococci, but longitudinal studies have shown that, in almost all cases, streptococci can be isolated initially, with staphylococci appearing later, presumably as secondary colonizing flora. In the past, penicillin was nearly always effective against these infections; in recent years, however, penicillin treatment failures have become more common, an observation suggesting that *S. aureus* infection may have become more prominent as a cause of impetigo. *Bullous impetigo* due to *S. aureus* is distinguished from typical streptococcal infection by the presence of more extensive, bullous lesions that break down and leave thin paper-like crusts instead of the thick amber crusts of streptococcal impetigo. Other skin lesions that may be confused with impetigo include herpetic lesions -- either those of orolabial herpes simplex or those of chickenpox or zoster. Herpetic lesions can generally be distinguished by their appearance as more discrete, grouped vesicles and by a positive Tzanck test. In difficult cases, cultures of vesicular fluid should yield group A streptococci in impetigo and the responsible virus in *Herpesvirus* infections.

**TREATMENT**

Treatment of streptococcal impetigo is the same as that for streptococcal pharyngitis. In view of evidence that *S. aureus* has become a relatively frequent cause of impetigo, empirical regimens should cover both streptococci and *S. aureus*. For example, either dicloxacillin or cephalexin can be given at a dose of 250 mg four times daily for 10 days. Topical mupirocin ointment is also effective. Rheumatic fever (unlike pharyngitis) is not a sequela to streptococcal skin infections, although poststreptococcal glomerulonephritis may follow either skin or throat infection. The reason for this difference is not known. One hypothesis is that the immune response necessary for development of rheumatic fever occurs only after infection of the pharyngeal mucosa. In addition, the strains of group A streptococci that cause pharyngitis are generally of different M protein types than those associated with skin infections; thus the strains that cause pharyngitis may have rheumatogenic potential, while the skin-infecting strains may not.

*Cellulitis* Inoculation of organisms into the skin may lead to infection involving the skin and subcutaneous tissues, or *cellulitis*. The portal of entry may be a traumatic or surgical wound, an insect bite, or any other break in skin integrity. Often, no entry site is apparent.

One form of streptococcal cellulitis, *erysipelas*, is characterized by a bright red appearance of the involved skin, which forms a plateau sharply demarcated from surrounding normal skin (Plate IID-34). The lesion is warm to the touch, may be tender, and appears shiny and swollen. The skin often has a *peau d'orange* texture, which is

thought to reflect involvement of superficial lymphatics; superficial blebs or bullae may form, usually 2 or 3 days after onset. The lesion typically develops over a few hours and is associated with fever and chills. Erysipelas tends to occur in certain characteristic locations: the malar area of the face (often with extension over the bridge of the nose to the contralateral malar region) and the lower extremities. After one episode, recurrence at the same site -- sometimes years later -- is not uncommon.

Classic cases of erysipelas, with the typical features described above, are almost always due tob-hemolytic streptococci, usually those of group A and occasionally those of group C or G. Often, however, the appearance of streptococcal cellulitis is not sufficiently distinctive to permit a specific diagnosis on clinical grounds. The area of involvement may not be one of the typical sites for erysipelas, the lesion may be less intensely red than usual and may fade into surrounding skin, and/or the patient may appear only mildly ill. In such cases, it is prudent to broaden the spectrum of empiric antimicrobial therapy to include other pathogens, particularly *S. aureus*, that can produce cellulitis with the same appearance. Staphylococcal infection should be suspected if cellulitis develops around a wound or ulcer.

Streptococcal cellulitis tends to develop at anatomic sites in which normal lymphatic drainage has been disrupted, such as sites of prior episodes of cellulitis, the arm ipsilateral to a mastectomy and axillary lymph node dissection, a lower extremity previously involved in deep venous thrombosis or chronic lymphedema, and the leg from which a saphenous vein has been harvested for coronary artery bypass grafting. The organism may enter via a breach in the dermal barrier at a location some distance from the eventual site of clinical cellulitis. For example, some patients with recurrent episodes of leg cellulitis following saphenous vein removal stop having recurrent episodes only after treatment of tinea pedis on the affected extremity, fissures in the skin presumably having served as a portal of entry for streptococci, which then produced infection more proximally in the leg at the site of previous injury. Streptococcal cellulitis may also involve recent surgical wounds. Group A streptococci are among the few bacterial pathogens that typically produce signs of wound infection and surrounding cellulitis within the first 24 h after surgery. These wound infections are usually associated with a thin exudate and may spread rapidly, either as cellulitis in the skin and subcutaneous tissue or as a deeper tissue infection (see below). Streptococcal wound infection or localized cellulitis may also be associated with *lymphangitis*, manifested by red streaks extending proximally along superficial lymphatics from the site of infection.

**TREATMENT**

SeeTable 140-2 andChap. 128.

*Deep Soft Tissue Infections Necrotizing fasciitis* (Fig. 18-CD4), also referred to as *hemolytic streptococcal gangrene*, is an infection involving the superficial and/or deep fascia investing the muscles of an extremity or the trunk. The source of the infection is either the skin, with organisms introduced into the tissue as a result of trauma (sometimes trivial), or the bowel flora, with organisms released during abdominal surgery or from an occult enteric source, such as a diverticular or appendiceal abscess. The site of inoculation in both forms of necrotizing fasciitis may be inapparent and is often some distance from the site of clinical involvement; e.g., the introduction of

organisms via minor trauma to the hand may be associated with clinical infection of the tissues overlying the shoulder or chest. In cases associated with the bowel flora, the infection is usually polymicrobial, involving a mixture of anaerobic bacteria (such as *Bacteroides fragilis* or anaerobic streptococci) and facultative organisms (usually gram-negative bacilli). Cases unrelated to contamination from bowel organisms are most commonly caused by group A streptococci, either alone or in combination with other organisms (most often *S. aureus*). Overall, group A streptococci are implicated in about 60% of cases of necrotizing fasciitis. The onset of symptoms is usually quite acute and is marked by severe pain at the site of involvement, malaise, fever, chills, and a toxic appearance. The physical findings, particularly early in the illness, may not be striking, with only minimal erythema of the overlying skin. Pain and tenderness are usually severe; in contrast, in more superficial cellulitis, the skin appearance is more abnormal, but pain and tenderness are only mild or moderate. As the infection progresses (often in a matter of several hours), the severity and extent of symptoms worsen, and skin changes become more evident, with the appearance of dusky or mottled erythema and edema. The marked tenderness of the involved area may evolve into anesthesia as the spreading inflammatory process produces infarction of cutaneous nerves.

Although myositis is more commonly due to *S. aureus* infection, group A streptococci occasionally produce abscesses in skeletal muscles (*streptococcal myositis*), with little or no involvement of the surrounding fascia or overlying skin. The presentation is usually subacute, but a fulminant form has been described in association with severe systemic toxicity, bacteremia, and a high mortality rate. The fulminant form may reflect the same basic disease process as that seen in necrotizing fasciitis, but with the necrotizing inflammatory process extending into the muscles themselves rather than remaining limited to the fascial layers.

## TREATMENT

Once necrotizing fasciitis is suspected, early surgical exploration is both diagnostically and therapeutically indicated. Surgery reveals necrosis and inflammatory fluid tracking along the fascial planes above and between muscle groups, without involvement of the muscles themselves. The process usually extends beyond the area of clinical involvement, and extensive debridement is required. Drainage and debridement are central to the management of necrotizing fasciitis; antibiotic treatment is a useful adjunct (Table 140-2), but surgery is life-saving.

Treatment for streptococcal myositis consists of surgical drainage -- usually by an open procedure that permits evaluation of the extent of the infection and ensures adequate debridement of involved tissues -- and high-dose penicillin (Table 140-2).

**Pneumonia and Empyema** Group A streptococci are an occasional cause of pneumonia, generally in previously healthy individuals. The onset of symptoms may be abrupt or gradual. Pleuritic chest pain, fever, chills, and dyspnea are the characteristic symptoms. Cough is usually present but may not be prominent. Approximately one-half of patients with group A streptococcal pneumonia have an accompanying pleural effusion. In contrast to the sterile parapneumonic effusions typical of pneumococcal pneumonia, those complicating streptococcal pneumonia are almost always infected.

The empyema fluid is usually visible by chest radiography on initial presentation and may enlarge rapidly. These pleural collections should be drained early, as they tend to become loculated rapidly, resulting in a chronic fibrotic reaction that may require thoracotomy for removal.

**Bacteremia, Puerperal Sepsis, and Streptococcal Toxic Shock Syndrome** Group A streptococcal bacteremia is usually associated with an identifiable local infection. Bacteremia occurs rarely with otherwise uncomplicated pharyngitis, occasionally with cellulitis or pneumonia, and relatively frequently with necrotizing fasciitis. Bacteremia without an identified source raises the possibility of endocarditis, an occult abscess, or osteomyelitis. A variety of focal infections may arise secondarily from streptococcal bacteremia, including endocarditis, meningitis, septic arthritis, osteomyelitis, peritonitis, and visceral abscesses.

Group A streptococci are occasionally implicated in infectious complications of childbirth, usually endometritis and associated bacteremia. In the preantibiotic era, puerperal sepsis was commonly caused by group A streptococci, but currently it is more often caused by group B streptococci. Several nosocomial outbreaks of puerperal infection due to group A streptococci have been traced to an asymptomatic carrier, usually an individual present at the delivery of the infant. The site of carriage may be the skin, throat, anus, or vagina.

Beginning in the late 1980s, several reports described patients who had group A streptococcal infections associated with shock and multisystem organ failure. This syndrome has been called the streptococcal toxic shock syndrome because it shares certain features with staphylococcal toxic shock syndrome. In 1993, a case definition for group A streptococcal toxic shock syndrome was formulated by a group of clinicians, microbiologists, and epidemiologists in conjunction with theCDC(Table 140-3). The general features of the illness include fever, hypotension, renal impairment, and respiratory distress syndrome. Various types of rash have been described, but rash usually does not develop. Laboratory abnormalities include a marked shift to the left in the white blood cell differential, with many immature granulocytes; hypocalcemia; hypoalbuminemia; and thrombocytopenia, which usually becomes more pronounced on the second or third day of illness. In contrast to those with staphylococcal toxic shock, the majority of patients with the streptococcal syndrome are bacteremic. The most common associated infection is a soft tissue infection -- necrotizing fasciitis, myositis, or cellulitis -- although a variety of other associated local infections have been described, including pneumonia, peritonitis, osteomyelitis, and myometritis. Streptococcal toxic shock syndrome is associated with a mortality rate of 30%, with most deaths secondary to shock and respiratory failure. Because of its rapidly progressive and lethal course, early recognition of the syndrome is essential. Patients should be given aggressive supportive care in the form of fluid resuscitation, pressors, and mechanical ventilation in addition to antimicrobial therapy and, in cases associated with necrotizing fasciitis, surgical debridement. Exactly why certain patients develop this fulminant syndrome is not known; however, early studies of the streptococcal strains isolated from these patients demonstrated a strong association with the production of pyrogenic exotoxin A. In subsequent case series, particularly from Europe, the syndrome was also associated with strains producing exotoxin B or C.

## TREATMENT

In light of the possible role of exotoxins or other streptococcal toxins in streptococcal toxic shock syndrome, treatment of the affected patients with clindamycin has been advocated by some authorities, who argue that, through its direct action on protein synthesis, clindamycin is more effective in rapidly terminating toxin production than penicillin -- a cell-wall agent. Support for this view comes from studies of an experimental model of streptococcal myositis, in which mice treated with clindamycin had a higher rate of survival than those given penicillin. Comparable data on the treatment of human infections are not available. Although clindamycin resistance in group A streptococci is uncommon (<2% among U.S. isolates), it has been documented. Thus, if clindamycin is used for initial treatment of a critically ill patient, penicillin should be given as well until the antibiotic susceptibility of the streptococcal isolate is known.

Intravenous immunoglobulin has been suggested as adjunctive therapy for streptococcal toxic shock; pooled immunoglobulin preparations are likely to contain antibodies capable of neutralizing the effects of streptococcal toxins. Anecdotal reports have suggested favorable clinical responses to intravenous immunoglobulin, but no controlled trials of this modality of therapy have yet been reported.

# STREPTOCOCCI OF GROUPS C AND G

Group C and group G streptococci are b-hemolytic bacteria that occasionally cause human infections similar to those caused by group A streptococci, including pharyngitis, cellulitis and soft-tissue infections, pneumonia, bacteremia, endocarditis, and septic arthritis. Puerperal sepsis, meningitis, epidural abscess, intraabdominal abscess, urinary tract infection, and neonatal sepsis have also been reported. Group C streptococci are a common cause of infection in domesticated animals, especially horses and cattle, and some human infections have been acquired through contact with animals or through consumption of unpasteurized milk. Bacteremia and septic arthritis more frequently involve group G than group C streptococci. Group C or G streptococcal bacteremia occurs most often in patients who are elderly or chronically ill and, in the absence of an obvious local infection, is likely to reflect endocarditis. Septic arthritis, sometimes involving multiple joints, may complicate endocarditis or develop in its absence.

## TREATMENT

Penicillin is the drug of choice for therapy of infections due to group C or G streptococci. Antibiotic treatment is the same as for patients with similar syndromes due to group A *Streptococcus* (Table 140-2). Patients with bacteremia or septic arthritis should receive intravenous penicillin (2 to 4 mU every 4 h). All group C and G streptococci are sensitive to penicillin; nearly all are inhibited in vitro by concentrations of £0.03 ug/mL. Occasional isolates exhibit tolerance: although inhibited by low concentrations of penicillin, they are killed only by significantly higher concentrations. The clinical significance of tolerance is unknown. Because of the poor clinical response of some patients to penicillin alone, the addition of gentamicin (1 mg/kg every 8 h for patients with normal renal function) is recommended by some authors for treatment of endocarditis or septic arthritis due to group C or G streptococci; however, combination therapy has not been shown to be

superior to treatment with penicillin alone.

Patients with joint infections often require repeated aspiration or open drainage and debridement for cure; the response to treatment may be slow, particularly in debilitated patients and those with involvement of more than one joint. Infection of prosthetic joints almost always requires removal of the prosthesis in addition to antibiotic therapy.

## GROUP B STREPTOCOCCI

Identified first as a cause of mastitis in cows, streptococci belonging to Lancefield's group B have since been recognized as a major cause of sepsis and meningitis in human neonates. Group B streptococci are also a frequent cause of peripartum fever in women and an occasional cause of serious infection in nonpregnant adults. Lancefield group B consists of a single species, *S. agalactiae*, which is definitively identified with specific antiserum to the group B cell wall-associated carbohydrate antigen. A streptococcal isolate can be classified presumptively as belonging to group B on the basis of biochemical tests, including hydrolysis of sodium hippurate (in which 99% of isolates are positive), hydrolysis of bile esculin agar (in which 99 to 100% are negative), bacitracin susceptibility (in which 92% are resistant), and production of CAMP factor (in which 98 to 100% are positive). CAMP factor is a phospholipase produced by group B streptococci that results in synergistic hemolysis with b lysin produced by certain strains of *S. aureus*. Its presence can be demonstrated by cross-streaking of the test isolate and an appropriate staphylococcal strain on a blood agar plate. Group B streptococci causing human infections are encapsulated by one of nine antigenically distinct polysaccharides. The capsular polysaccharide has been shown experimentally to be important in the virulence of the organism. Antibodies to the capsular polysaccharide afford protection against group B streptococci of the same (but not of a different) capsular type.

### INFECTION IN NEONATES

Two general types of group B streptococcal infection in infants are defined by the age of the patient at presentation. *Early-onset infections* occur within the first week of life, with a median age of 20 h at the onset of illness. Approximately half of these infants have signs of group B streptococcal disease at birth. The infection is acquired during or shortly before birth from organisms colonizing the maternal genital tract. Surveillance studies have shown that 5 to 40% of women are vaginal or rectal carriers of group B streptococci. Approximately 50% of infants delivered vaginally by carrier mothers become colonized, although only 1 to 2% of those colonized develop clinically evident infection. Prematurity and maternal risk factors (prolonged labor, obstetric complications, and maternal fever) are often involved. The presentation of early-onset infection is the same as that of other forms of neonatal sepsis. Typical findings include respiratory distress, lethargy, and hypotension. Essentially all infants with early-onset disease are bacteremic, one-third to one-half have pneumonia and/or respiratory distress syndrome, and one-third have meningitis.

*Late-onset infections* occur in infants between 1 week and 3 months of age, with a mean age at onset of 3 to 4 weeks. The infecting organism may be acquired during delivery (as in early-onset cases) or during later contact with a colonized mother,

nursery personnel, or another source. Meningitis is the most common manifestation of late-onset infection and in most cases is associated with a strain of capsular type III. Infants present with fever, lethargy or irritability, poor feeding, and seizures. The various other types of late-onset infection include bacteremia without an identified source, osteomyelitis, septic arthritis, and facial cellulitis associated with submandibular or preauricular adenitis.

## TREATMENT

Penicillin is the treatment of choice for all group B streptococcal infections. Empirical broad-spectrum therapy for suspected bacterial sepsis, consisting of ampicillin and gentamicin, is generally administered until culture results become available. If cultures yield group B streptococci, many pediatricians continue to administer gentamicin, along with ampicillin or penicillin, for a few days until clinical improvement becomes evident. Infants with bacteremia or soft-tissue infection should receive penicillin at a dosage of 200,000 units/kg per day in divided doses; those with meningitis should receive 400,000 units/kg per day. Meningitis should be treated for at least 14 days because of the risk of relapse with shorter courses.

**Prevention** The incidence of group B streptococcal infection is unusually high among infants of women with risk factors: preterm delivery, early rupture of membranes (>24 h before delivery), prolonged labor, fever, or chorioamnionitis. Because the usual source of the organisms infecting a neonate is the mother's birth canal, efforts have been made to prevent group B streptococcal infections by the identification of high-risk carrier mothers and their treatment with various forms of antibiotic or immunoprophylaxis. Prophylactic administration of ampicillin or penicillin to such patients during delivery has been shown to reduce the risk of infection in the newborn. This approach has been hampered by the logistical difficulties of identifying colonized women before delivery, since the results of vaginal cultures early in pregnancy are poor predictors of carrier status at delivery. TheCDC has suggested two alternative approaches to the prevention of neonatal group B streptococcal infection: In the first approach, women are screened for anogenital colonization at 35 to 37 weeks of pregnancy by means of a swab culture of the lower vagina and anorectum; intrapartum chemoprophylaxis is offered to carriers and is *recommended* for those carriers with any of the risk factors noted above, those anticipating multiple births, and those who have previously given birth to an infant with group B streptococcal infection. In the second approach, screening cultures need not be performed, but intrapartum chemoprophylaxis is recommended for *all* women with one or more of the risk factors noted above. The recommended regimen for chemoprophylaxis is 5 million units of penicillin G followed by 2.5 million units every 4 h until delivery. Clindamycin or erythromycin may be substituted in women allergic to penicillin.

Treatment of all pregnant women who are colonized or who have risk factors for neonatal infection will result in exposure of 15 to 25% of pregnant women and newborns to antibiotics, with the attendant risks of allergic reactions and selection for resistant organisms. Although still in the developmental stages, a group B streptococcal vaccine may ultimately offer a better solution to prevention. Because transplacental passage of maternal antibodies produces protective antibody levels in the newborn, efforts are under way to develop a vaccine against group B streptococci that can be given to

childbearing women before or during pregnancy. Results of phase 1 clinical trials of group B streptococcal capsular polysaccharide-protein conjugate vaccines suggest that a multivalent conjugate vaccine would be safe and highly immunogenic.

### INFECTION IN ADULTS

The majority of group B streptococcal infections in adults are related to pregnancy and parturition. Peripartum fever, the most common manifestation, is sometimes accompanied by symptoms and signs of endometritis or chorioamnionitis (abdominal distention and uterine or adnexal tenderness). Blood cultures are often positive, as are cultures of vaginal swabs. Bacteremia is usually transitory but occasionally results in meningitis or endocarditis. Infections in adults that are not associated with the peripartum period generally involve individuals who are elderly or have some underlying chronic illness, such as diabetes mellitus or a malignancy. Among the infections that develop with some frequency in adults are cellulitis and soft tissue infection (including infected diabetic skin ulcers), urinary tract infection, pneumonia, endocarditis, and septic arthritis. Other reported infections include meningitis, osteomyelitis, and intraabdominal or pelvic abscesses.

### TREATMENT

Group B streptococci are less sensitive to penicillin than group A organisms, requiring somewhat higher doses. Adults with serious localized infections (pneumonia, pyelonephritis, abscess) should receive doses in the range of 12 million units of penicillin G daily, while patients with endocarditis or meningitis should receive 18 to 24 million units per day in divided doses. Vancomycin is an acceptable alternative for patients allergic to penicillin.

## ENTEROCOCCI, GROUP D STREPTOCOCCI

### ENTEROCOCCI

Lancefield group D includes the enterococci, organisms now classified in a separate genus from other streptococci, and nonenterococcal group D streptococci. Enterococci are distinguished from nonenterococcal group D streptococci by their ability to grow in the presence of 6.5% sodium chloride and by the results of other biochemical tests. The enterococcal species that are significant pathogens for humans are *E. faecalis* and *E. faecium*. These organisms tend to produce infection in patients who are elderly or debilitated or in whom mucosal or epithelial barriers have been disrupted or the balance of the normal flora altered by antibiotic treatment. Urinary tract infections due to enterococci are quite common, particularly among patients who have received antibiotic treatment or undergone instrumentation of the urinary tract. Enterococci are a frequent cause of nosocomial bacteremia in patients with intravascular catheters. These organisms account for 10 to 20% of cases of bacterial endocarditis on both native and prosthetic valves. The presentation of enterococcal endocarditis is usually subacute but may be acute, with rapidly progressive valve destruction. Enterococci are frequently cultured from bile and are involved in infectious complications of biliary surgery and in liver abscesses. Moreover, enterococci are often isolated from polymicrobial infections arising from the bowel flora (e.g., intraabdominal abscesses), from abdominal surgical

wounds, and from diabetic foot ulcers. While such mixed infections are frequently cured by antimicrobials not active against enterococci, specific therapy directed against enterococci is warranted when these organisms are the predominant species or are isolated from blood cultures.

## TREATMENT

Unlike other streptococci, enterococci are not reliably killed by penicillin or ampicillin alone at concentrations achieved clinically in the blood or tissues. Ampicillin reaches sufficiently high urinary concentrations to constitute adequate monotherapy for uncomplicated urinary tract infections. Because in vitro testing has shown evidence of synergistic killing of most enterococcal strains by the combination of penicillin or ampicillin with an aminoglycoside, combined therapy is recommended for enterococcal endocarditis and meningitis; the regimen is penicillin (3 to 4 million units every 4 h) or ampicillin (2 g every 4 h) plus moderate-dose gentamicin (1 mg/kg every 8 h for patients with normal renal function). Enterococcal endocarditis should be treated for a minimum of 4 weeks and for 6 weeks if symptoms have been present for³3 months or if the infection involves a prosthetic heart valve. For nonendocarditis bacteremia and other serious enterococcal infections, it is not known whether the efficacy of single-agentb-lactam therapy is improved by the addition of gentamicin, but many infectious disease specialists use combination therapy for such infections, especially in critically ill patients. Vancomycin, in combination with gentamicin, may be substituted for penicillin in allergic patients. Enterococci are resistant to all cephalosporins; therefore, this class of antibiotics should not be used for treatment of enterococcal infections.

Antimicrobial susceptibility testing should be performed routinely on enterococcal isolates from patients with serious infections, and therapy should be adjusted according to the results (Table 140-4). Most enterococci are resistant to streptomycin, and this drug should not be used for treatment of enterococcal infection unless in vitro testing of the strain indicates susceptibility. Though less widespread than streptomycin resistance, high-level resistance to gentamicin -- with a minimum inhibitory concentration (MIC) of >2000 ug/mL -- has become common. Gentamicin-resistant enterococci should be tested for susceptibility to streptomycin; occasional gentamicin-resistant enterococci are sensitive to streptomycin. If the isolate is resistant to all aminoglycosides, treatment with penicillin or ampicillin alone may be successful. The prolonged administration (i.e., for at least 6 weeks) of high-dose ampicillin (e.g., 12 g/d) is recommended for endocarditis due to these highly resistant enterococci.

Enterococci may be resistant to penicillins via two distinct mechanisms. The first is the production ofb-lactamase (mediating resistance to penicillin and ampicillin), which has been reported for *E. faecalis* isolates from several locations in the United States and other countries. Because the amount of b-lactamase produced by enterococci may be insufficient for detection by routine antibiotic susceptibility testing, isolates from serious infections should be screened specifically forb-lactamase production with use of a chromogenic cephalosporin or by another method. For the treatment ofb-lactamase-producing strains, vancomycin, ampicillin/sulbactam, amoxicillin/clavulanate, or imipenem may be used in combination with gentamicin.

The second mechanism of penicillin resistance is not mediated byb-lactamase and may

be due to altered penicillin-binding proteins. This intrinsic penicillin resistance is common among *E. faecium* isolates, which routinely are more resistant tob-lactam antibiotics than are isolates of *E. faecalis*. Moderately resistant enterococci (MICs of penicillin and ampicillin, 16 to 64 ug/mL) may be susceptible to high-dose penicillin or ampicillin plus gentamicin, but strains with MICs of³200 ug/mL must be considered resistant to clinically achievable levels of b-lactam antibiotics, including imipenem. Vancomycin plus gentamicin is the recommended regimen for infections due to enterococci with high-level intrinsic resistance tob-lactams.

Vancomycin-resistant enterococci, first reported from clinical sources in the late 1980s, have become common in many hospitals. Three major vancomycin resistance phenotypes have been described: VanA, VanB, and VanC. The VanA phenotype is associated with high-level resistance to vancomycin and to teicoplanin, a related glycopeptide antibiotic not currently available in the United States. VanB and VanC strains are resistant to vancomycin but susceptible to teicoplanin, although teicoplanin resistance may develop during treatment in VanB strains. For enterococci resistant to both vancomycin and b-lactams, there are no established therapies. Regimens that have been tried with some success in individual cases or experimentally include ciprofloxacin plus rifampin plus gentamicin; ampicillin plus vancomycin (particularly if in vitro testing shows synergistic bacteriostatic activity); and chloramphenicol or tetracycline (if the strain is susceptible in vitro). Quinupristin/dalfopristin (Synercid) is a streptogramin combination with in vitro activity against *E. faecium*, including vancomycin-resistant isolates, but not against *E. faecalis* or other enterococcal species. The evidence for clinical efficacy of this agent in serious enterococcal infections is limited, and, as of this writing, quinupristin/dalfopristin is not yet licensed for use in the United States.

### OTHER GROUP D STREPTOCOCCI

The main nonenterococcal group D streptococcal species that causes human infections is *S. bovis*. *S. bovis* endocarditis is often associated with neoplasms of the gastrointestinal tract -- most frequently a colon carcinoma or polyp -- but is also reported in association with other bowel lesions. When occult gastrointestinal lesions are carefully sought, abnormalities are found in ³60% of patients with *S. bovis* endocarditis. In contrast to the enterococci, nonenterococcal group D streptococci like *S. bovis* are reliably killed by penicillin as a single agent, and penicillin is the treatment of choice for *S. bovis* infections.

## VIRIDANS AND OTHER STREPTOCOCCI

### VIRIDANS STREPTOCOCCI

Consisting of multiple species of a-hemolytic streptococci, the viridans streptococci are a heterogeneous group of organisms that are important as agents of bacterial endocarditis (Chap. 126). Several species of viridans streptococci, including *S. salivarius*, *S. mitis*, *S. sanguis*, and *S. mutans*, are part of the normal flora of the mouth, where they live in close association with the teeth and gingiva. Some species contribute to the development of dental caries. The transient viridans streptococcal bacteremia induced by eating, tooth-brushing, flossing, and other sources of minor trauma, together

with adherence to biologic surfaces, is thought to account for the predilection of these organisms to cause endocarditis. Viridans streptococci are also isolated, often as part of a mixed flora, from sites of sinusitis, brain abscess, and liver abscess.

Viridans streptococcal bacteremia occurs relatively frequently in neutropenic patients, particularly after bone marrow transplantation or high-dose chemotherapy for cancer. Some of these patients develop a sepsis syndrome with high fever and shock. Risk factors for viridans streptococcal bacteremia include chemotherapy with high-dose cytosine arabinoside, prior treatment with trimethoprim-sulfamethoxazole or a fluoroquinolone, treatment with antacids or histamine antagonists, mucositis, and profound neutropenia.

The *S. milleri* group (also referred to as the *S. intermedius* or *S. anginosus* group) includes three species that cause human disease: *S. intermedius*, *S. anginosus*, and *S. constellatus*. These organisms are often are considered viridans streptococci, although they differ somewhat from other viridans streptococci in both their hemolytic pattern (they may bea-, b-, or nonhemolytic) and the disease syndromes they cause. This group commonly produces suppurative infections, particularly abscesses of brain and abdominal viscera, and infections related to the oral cavity or respiratory tract, such as peritonsillar abscess, lung abscess, and empyema.

## TREATMENT

Isolates from neutropenic patients with bacteremia often are resistant to penicillin; thus these patients should be treated presumptively with vancomycin until the results of susceptibility testing become available. Viridans streptococci isolated in other clinical settings usually are sensitive to penicillin.

## NUTRITIONALLY VARIANT STREPTOCOCCI

Occasional isolates cultured from the blood of patients with endocarditis fail to grow when subcultured on solid media. These *nutritionally variant streptococci* require supplemental thiol compounds or active forms of vitamin $B_6$(pyridoxal or pyridoxamine) for growth in the laboratory. The nutritionally variant streptococci are generally grouped with the viridans streptococci because they cause similar types of infections. However, they have been reclassified on the basis of 16S RNA sequence comparisons into a separate genus, *Abiotrophia*, with two species: *A. defectivus* and *A. adjacens*.

## TREATMENT

Because treatment failure and relapse appear to be more common for cases of endocarditis due to nutritionally variant streptococci than for usual viridans streptococci, the addition of gentamicin (1 mg/kg every 8 h for patients with normal renal function) to the penicillin regimen is recommended in therapy for endocarditis due to these organisms.

## OTHER STREPTOCOCCI

*S. suis* is an important pathogen in swine and has been reported to cause meningitis in

humans, usually in individuals with occupational exposure to pigs. Strains of *S. suis* associated with human infections have generally reacted with Lancefield group R typing serum and sometimes with group D typing serum as well. Isolates may bea- or b-hemolytic and are sensitive to penicillin. *S. iniae*, a pathogen of fish, has been associated with infections in humans who have handled live or freshly killed fish. Cellulitis of the hand is the most common form of human infection, although bacteremia and endocarditis have been reported. *Anaerobic streptococci*, or *peptostreptococci*, are part of the normal flora of the oral cavity, bowel, and vagina. Infections caused by the anaerobic streptococci are discussed in Chap. 167.

(Bibliography omitted in Palm version)

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Back to Table of Contents

# 141. DIPHTHERIA, OTHER CORYNEBACTERIAL INFECTIONS, AND ANTHRAX - *Randall K. Holmes*

## DIPHTHERIA

### DEFINITION

Diphtheria is a localized infection of mucous membranes or skin caused by *Corynebacterium diphtheriae*. A characteristic pseudomembrane may be present at the site of infection (Fig. 141-CD1). Some strains of *C. diphtheriae* produce diphtheria toxin, a protein that can cause myocarditis, polyneuritis, and other systemic toxic effects. Respiratory diphtheria is usually caused by toxinogenic (*tox*$^+$) *C. diphtheriae*, but cutaneous diphtheria is frequently caused by nontoxinogenic (*tox*$^-$) strains.

### ETIOLOGY

*C. diphtheriae* is an aerobic, nonmotile, nonsporulating, irregularly staining, gram-positive rod. The bacteria are club-shaped and are often arranged in clusters (*Chinese letters*) or parallel arrays (*palisades*). *C. diphtheriae* forms gray to black colonies on selective media containing tellurite. The gravis, mitis, and intermedius biotypes are distinguished by colonial morphology and laboratory tests. Both *tox*$^+$ and *tox*$^-$ strains cause infections, and *tox*$^+$ strains of all three biotypes can cause severe disease. The gene for diphtheria toxin is present in specific corynephages, and *tox*$^-$ *C. diphtheriae* can acquire the ability to produce diphtheria toxin by infection with *tox*$^+$phages (*phage conversion*). Growth of *C. diphtheriae* under low-iron conditions that mimic the environment of host tissues induces production of diphtheria toxin and expression of systems for siderophore-dependent iron uptake and utilization of iron from heme.

### IMMUNOLOGY

Treatment of diphtheria toxin with formaldehyde converts it to a nontoxic but immunogenic product (*diphtheria toxoid*). Immunization with toxoid elicits antibody (*antitoxin*) that neutralizes the toxin and prevents diphtheria. The attack rate and mortality rate for diphtheria are low in immune individuals with antitoxin titers of >0.01 unit per milliliter. Antitoxin neither prevents colonization by *C. diphtheriae* nor eradicates the *carrier state*. When most individuals in a population have protective levels of antitoxin (*herd immunity*), the carrier rate for *tox*$^+$ strains of *C. diphtheriae* falls to a low level, and the risk that susceptible individuals will be exposed to *tox*$^+$ *C. diphtheriae* decreases dramatically. Susceptible individuals may contract diphtheria if they travel to regions where the disease is present or if *tox*$^+$ strains of *C. diphtheriae* are introduced into their community.

### EPIDEMIOLOGY AND IMMUNITY

Humans are the principal reservoir for *C. diphtheriae*. Transmission occurs primarily by close personal contact. The risk is greater that *C. diphtheriae* will be transmitted to susceptible individuals from patients with diphtheria than from carriers. The incubation period for respiratory diphtheria is typically 2 to 5 days and rarely up to 8 days.

Cutaneous diphtheria is usually a secondary infection whose signs develop an average of 7 days (range, 1 to >21 days) after the appearance of primary dermatologic lesions of other etiologies.

In temperate climates, diphtheria primarily involves the respiratory tract; occurs throughout the year, with a peak incidence in colder months; and is usually caused by *tox*+ *C. diphtheriae*. Before immunization was introduced, diphtheria was primarily a disease of children; it affected up to 10% of individuals in this group and sometimes caused devastating epidemics. Most young infants were immune because of transplacental transfer of maternal IgG antitoxin, but children became susceptible by 6 to 12 months of age. Approximately 75% of individuals became immune by age 10 as a result of contact with *C. diphtheriae*. Mortality rates of 30 to 40% were common in untreated disease and were sometimes >50% in epidemics. Treatment with antitoxin reduced the case-fatality rate to 5 to 10%.

Routine immunization of children in the United States resulted in a progressive decrease of diphtheria from the peak of 206,939 cases (incidence rate, 191 cases per 100,000 population) in 1921 to <5 cases per year since 1980. Concomitantly, circulation of *tox*+ strains of *C. diphtheriae* among the population decreased dramatically, although an endemic focus for transmission of *tox*+ and *tox*- strains without clinical disease was recently identified in North Dakota. As the incidence rate of diphtheria decreased, a higher proportion of cases occurred in older persons (who were never immunized or whose immunity waned because it was not boosted by either booster doses of vaccine or contact with *C. diphtheriae*), but the case-fatality ratio remained unchanged at 5 to 10%. High rates of immunization are currently achieved by school entry (>96%), but immunization rates for younger children are substantially lower. Among adults >20 years of age, 19 to 77% are susceptible as a consequence of failure to receive periodic booster immunizations and lack of contact with *C. diphtheriae*. The most recent large diphtheria outbreak in the United States (about 1100 cases) occurred in Seattle, Washington, between 1972 and 1982. Alcoholism, low socioeconomic status, crowded living conditions, and Native-American ethnic background were significant risk factors in this outbreak.

A massive diphtheria epidemic (>157,000 cases and 5000 deaths) occurred recently in the states of the former Soviet Union and accounted for>80% of diphtheria cases reported worldwide during that interval. The epidemic began in 1990 with 1436 cases (0.49 per 100,000 population), peaked in 1995 with 50,425 cases (17.29 per 100,000 population), and waned by 1998 with 2720 cases (0.93 per 100,000 population) as the result of a mass immunization program. The progression of the epidemic was associated with emergence of a previously uncommon clonal group of *tox*+ *C. diphtheriae* strains that accounted for>80% of isolates by 1994; molecular analysis of the *tox* gene from these strains demonstrated that the existing diphtheria toxoid vaccine remained appropriate for control of the epidemic by vaccination.

A majority of cases throughout this epidemic occurred in persons ³15 years old, and adults from 40 to 49 years old had very high incidence and death rates. In 1994, case-fatality rates varied from 2.8%in the Russian Federation to 23% in Lithuania and Turkmenistan. Factors that facilitated the spread of this epidemic included large-scale population movements, socioeconomic instability, deteriorating health infrastructure,

delayed implementation of aggressive control measures in response to the epidemic, inadequate information for physicians and the public, and frequent shortages of supplies for prevention and treatment of the disease. The most important risk factor for diphtheria in the Republic of Georgia was lack of vaccination (matched odds ratio, 19.2), but household diphtheria exposure, exposure to skin lesions, the presence of tonsils, a history of eczema, preceding fever with myalgia, sharing a bed, sharing glasses and cups, and taking a bath less often than weekly were also significant risk factors. Although small numbers of imported cases from this epidemic occurred in western European countries, none resulted in secondary transmission of diphtheria, notwithstanding a high proportion of susceptible adults in countries with imported cases. Inadequate primary immunization of children in the states of the former Soviet Union in the years preceding the epidemic, along with failure to maintain adequate immunity in adults by booster immunization, may have synergistically facilitated transmission of diphtheria and emergence of the massive epidemic in this region.

In the tropics, cutaneous diphtheria is more common than respiratory diphtheria, occurs throughout the year, and often develops as a secondary infection complicating other dermatoses. Isolates of *C. diphtheriae* from skin lesions are more often *tox*$^-$than *tox*$^+$. Cutaneous diphtheria is increasingly recognized in temperate climates and accounted for 86% of the 1100 cases in the Seattle epidemic of 1972 to 1982. Since 1980, cutaneous diphtheria has not been a reportable disease in the United States, and recent health statistics include only respiratory diphtheria.

During the 1990s, *tox*$^-$ strains of *C. diphtheriae* were associated with new types of infections. In the United Kingdom, these strains caused symptomatic pharyngitis, predominantly among homosexual men, that was sometimes accompanied by tonsillar exudate. In Switzerland, strains with a high potential for invasiveness were isolated from 38 intravenous drug users and shown by ribotyping to be clonally related. The latter strains caused infections of the skin (15 cases), respiratory tract (10 cases), and blood (13 cases). Among the patients with bloodstream infections, 9 had endocarditis, and 4 of these 9 patients died.

## PATHOLOGY AND PATHOGENESIS

*C. diphtheriae* infects mucous membranes, most commonly in the respiratory tract, and also invades open skin lesions resulting from insect bites or trauma. In infections caused by *tox*$^+$ *C. diphtheriae*, initial edema and hyperemia are often followed by epithelial necrosis and acute inflammation. Coagulation of the dense fibrinopurulent exudate produces a pseudomembrane, and the inflammatory reaction accompanied by vascular congestion extends into the underlying tissues. The pseudomembrane contains large numbers of *C. diphtheriae* organisms, but the bacteria are rarely isolated from the blood or internal organs.

Diphtheria toxin acts both locally and systemically, and the lethal dose for humans is ~0.1 ug/kg. Toxin contributes locally to pseudomembrane formation; systemically, it can cause myocarditis, neuritis, and focal necrosis in various organs, including the kidneys, liver, and adrenal glands. Changes in the myocardium include cloudy swelling of muscle fibers and interstitial edema. These changes are followed within weeks by hyaline and granular degeneration (sometimes with fatty degeneration), progressing to myolysis and

finally to the replacement of lost muscle by fibrosis. Thus, diphtheria can cause permanent cardiac damage. In diphtheritic polyneuritis, pathologic changes include patchy breakdown of myelin sheaths in peripheral and autonomic nerves, but recovery of nerve damage is the rule if the patient survives.

Diphtheria toxin is produced by *C. diphtheriae* as an extracellular polypeptide. Proteolytic cleavage forms nicked toxin consisting of fragments A and B. Fragment B binds to a plasma-membrane receptor (a precursor of a heparin-binding growth factor resembling epidermal growth factor), and the bound toxin is internalized by receptor-mediated endocytosis. Fragment A is translocated across the endosomal membrane and released into the cytoplasm, where it catalyzes the transfer of the adenosine diphosphate ribose moiety from nicotinamide adenine dinucleotide (NAD) to a modified histidine residue (diphthamide) on elongation factor 2 (EF-2), thereby inactivating EF-2 and inhibiting protein synthesis. One molecule of fragment A in the cytoplasm can kill a cell. Other metabolic alterations are secondary to inhibition of protein synthesis.

## CLINICAL MANIFESTATIONS

Patients with *C. diphtheriae* in the respiratory tract are classified as diphtheria cases if pseudomembranes are present and as diphtheria carriers if pseudomembranes are absent. The disease is graded as *tonsillar* if pseudomembranes are localized to the tonsils, as *combined types* or *delayed diagnosis* if more extensive pseudomembranes are present, and as *severe* if cervical adenopathy or cervical edema is also present. Onset is often gradual, but most patients seek medical care within a few days of becoming ill. Fever of 37.8° to 38.9°C (100° to 102°F), sore throat, and weakness are the most common symptoms, while dysphagia, headache, and change of voice occur in fewer than half of patients. Neck edema and difficulty breathing are noted in£10% of patients and are associated with an increased risk of death. Systemic manifestations are due primarily to toxic effects of diphtheria toxin. Patients without toxicity exhibit discomfort and malaise associated with local infection, whereas severely toxic patients may develop listlessness, pallor, and tachycardia that can progress rapidly to vascular collapse.

Primary infection in the respiratory tract is most often tonsillopharyngeal but may also be (in decreasing order) laryngeal, nasal, and tracheobronchial. Multiple sites are frequently involved, and secondary spread of pharyngeal infection upward to the nasal mucosa or downward to the larynx and tracheobronchial tree is much more common than primary infection at those sites. Systemic toxicity is usually most severe when extensive pseudomembrane extends from the tonsils and pharynx into contiguous regions. A small percentage of patients present with malignant or "bull-neck" diphtheria, with extensive pseudomembrane formation, foul breath, massive swelling of the tonsils and uvula, thick speech, cervical lymphadenopathy, striking edematous swelling of the submandibular region and anterior neck, and severe toxicity.

In tonsillopharyngeal diphtheria, isolated spots of gray or white exudate may appear first. These spots often extend and coalesce within a day to form a confluent, sharply demarcated pseudomembrane that becomes progressively thicker, more tightly adherent to the underlying tissue, and darker gray in color. Unlike the exudate in

streptococcal pharyngitis, the diphtheritic pseudomembrane often extends beyond the margin of the tonsils onto the tonsillar pillars, palate, or uvula. Dislodging the membrane is likely to cause bleeding. Laryngeal diphtheria often presents as hoarseness and cough. Demonstration of laryngeal pseudomembrane by laryngoscopy helps distinguish diphtheria from other infectious forms of laryngitis. Patients with nasal diphtheria may present with unilateral or bilateral serosanguineous nasal discharge associated with irritation of the nares or lip. Primary or secondary diphtheritic infection occasionally involves other mucous membranes, including the conjunctiva and the membranes of the genitourinary and gastrointestinal tracts.

Cutaneous diphtheria usually presents as an infection by *C. diphtheriae* of preexisting dermatoses involving the lower extremities, upper extremities, head, or trunk. The clinical features are similar to those of other secondary cutaneous bacterial infections. In the tropics, cutaneous diphtheria may present as a primary cutaneous lesion, typically with morphologically distinct "punched-out" ulcers that are covered by necrotic slough or membrane and have well-demarcated edges.

*C. diphtheriae* is an occasional cause of invasive infections, including endocarditis and septic arthritis. Risk factors for such infections include preexisting cardiac abnormalities, abuse of intravenous drugs, and alcoholic cirrhosis.

**COMPLICATIONS**

Obstruction of the respiratory tract can be caused by extensive pseudomembrane formation and swelling early in the disease or by sloughed pseudomembrane that becomes lodged in the airways later in the disease. The risk is greater when infection involves the larynx or the tracheobronchial tree and in children because of the small size of the airways.

Myocarditis and polyneuritis are the most prominent toxic manifestations of diphtheria. The risk of each is proportional to the severity of local disease. Myocarditis occurred in 22% and neuritis in 5% of 656 hospitalized patients (54% female, 70% ³15 years old) with diphtheria in the Kyrgyz Republic in 1995; 7% of patients with myocarditis and 2% of patients without myocarditis died. The median interval from hospitalization to death was 4.5 days (range, 0 to 13 days).

Bulbar dysfunction in diphtheritic neuritis typically develops during the first 2 weeks. Palatal and pharyngeal paralysis usually develops first. Swallowing is difficult, the voice is nasal, and ingested fluids may be regurgitated through the nose. Additional bulbar signs may develop over several weeks, with oculomotor and ciliary paralysis more common than facial or laryngeal paralysis. Peripheral polyneuritis typically begins from 1 to 3 months after the onset of diphtheria with proximal weakness of the extremities, which spreads distally. Paresthesia may occur, most often in a glove-and-stocking distribution. Polyneuritis usually resolves completely, with the time needed for improvement approximately equal to that elapsing from exposure to the development of symptoms.

Pneumonia occurs in more than one-half of fatal cases of diphtheria. Less common complications include renal failure, encephalitis, cerebral infarction, pulmonary

embolism, and bacteremia or endocarditis due to invasive infection by *C. diphtheriae*. Serum sickness may result from antitoxin therapy.

## COURSE AND PROGNOSIS

Most cases of diphtheria develop in nonimmunized patients. The attack rate, severity of disease, and risk of complications are much lower in immunized patients. The pseudomembrane may continue to increase in size during the first day after administration of antitoxin. During the next several days to a week, it becomes softer, less adherent, and nonconfluent and eventually disappears. In the preantibiotic era, *C. diphtheriae* persisted in the throat for ~2 weeks in one-half of patients and for ³1 month in about one-fifth. Mortality increases with the severity of local disease, the extent of pseudomembrane formation, and the delay between onset of local disease and administration of antitoxin. The death rate is highest during the first week of illness; among patients with bull-neck diphtheria; among patients with myocarditis who develop ventricular tachycardia, atrial fibrillation, or complete heart block; among patients with laryngeal or tracheobronchial involvement; among infants and patients >60 years of age; and among alcoholics. Both the mortality rate and the risk of myocarditis or peripheral neuropathy are significantly lower in cutaneous diphtheria than in respiratory diphtheria.

## DIAGNOSIS

A characteristic pseudomembrane on the mucosa of the tonsils, palate, oropharynx, nasopharynx, nose, or larynx suggests diphtheria but is not uniformly present. Diphtheritic pseudomembrane must be distinguished from other pharyngeal exudates, including those of group A b-hemolytic streptococcal infections, infectious mononucleosis, viral pharyngitis, fusospirochetal infection, and candidiasis. Diphtheria should be considered in patients with sore throat, cervical adenopathy or swelling, and low-grade fever, especially when these manifestations are accompanied by systemic toxicity, hoarseness, stridor, palatal paralysis, or serosanguineous nasal discharge with or without demonstrable pseudomembrane. Treatment with diphtheria antitoxin should begin as soon as the clinical diagnosis of diphtheria is made.

Definitive diagnosis of diphtheria depends on the isolation of *C. diphtheriae* from local lesions. The laboratory should be notified that diphtheria is suspected to ensure the use of selective tellurite medium appropriate for the isolation of *C. diphtheriae*. All isolates of *C. diphtheriae* should be subjected to toxicity testing. Primary isolates can be screened rapidly for the presence of the *tox* gene by the polymerase chain reaction, although occasional strains of *C. diphtheriae* that carry an inactive toxin gene give false-positive results. Biochemical tests needed to differentiate *C. diphtheriae* from corynebacteria of the normal flora (diphtheroids) require several days. Group A b-hemolytic streptococci and *Staphylococcus aureus* are also isolated frequently from patients with diphtheria.

Cutaneous diphtheria may present as a characteristic "punched-out" ulcer with a membrane, but it is more often indistinguishable from other inflammatory dermatoses. Diagnosis depends on a high degree of suspicion and on culture of cutaneous lesions on laboratory media appropriate for isolation of *C. diphtheriae*. Throat samples from all patients with cutaneous diphtheria should be cultured for *C. diphtheriae*.

## TREATMENT

The decision to administer diphtheria antitoxin must be based on the clinical diagnosis of diphtheria without definitive laboratory confirmation, since each day of delay in treatment is associated with increased mortality. Because diphtheria antitoxin is produced in horses, it is necessary to inquire about possible allergy to horse serum and to perform a conjunctival or intracutaneous test with diluted antitoxin for immediate hypersensitivity. Epinephrine must be available for immediate administration to patients with severe allergic reactions. Patients with immediate hypersensitivity should be desensitized before a full therapeutic dose of antitoxin is given. The dose of diphtheria antitoxin currently recommended by the Committee on Infectious Diseases of the American Academy of Pediatrics is based on the site of the primary infection and the duration and severity of disease: 20,000 to 40,000 units for disease that has been present for £48 h and involves the pharynx or larynx; 40,000 to 60,000 units for nasopharyngeal infections; and 80,000 to 100,000 units for disease that is extensive, has been present for³3 days, or is accompanied by diffuse swelling of the neck. Antitoxin is administered intravenously by infusion in saline over 60 min to neutralize unbound toxin rapidly. The ~10% risk of serum sickness is acceptable because of the established therapeutic value of antitoxin in decreasing mortality from respiratory diphtheria. The risk of systemic toxicity is lower in cutaneous diphtheria than in respiratory diphtheria and must be weighed against the potential adverse effects of antitoxin treatment; authorities are not unanimous in recommending antitoxin therapy for cutaneous diphtheria.

Antibiotics have little demonstrated effect on the healing of local infection in diphtheria patients treated with antitoxin. The primary goal of antibiotic therapy for patients or carriers is therefore to eradicate *C. diphtheriae* and prevent its transmission from the patient to susceptible contacts. Erythromycin, penicillin G, rifampin, or clindamycin is recommended by most authorities. Commonly recommended regimens for the treatment of adults with respiratory diphtheria are erythromycin (500 mg four times daily, given parenterally or orally) or intramuscular procaine penicillin G (600,000 units at 12-h intervals) for 14 days. Patients with cutaneous diphtheria and carriers can be treated orally with erythromycin (500 mg four times daily) or rifampin (600 mg once daily) for 7 days. If compliance is in question, a single dose of benzathine penicillin G (1.2 to 2.4 million units intramuscularly) can be substituted. Eradication of *C. diphtheriae* should be documented by negative cultures of samples taken on two or three successive days, beginning at least 24 h after the completion of antibiotic therapy. Some authorities also recommend a repeat throat culture 2 weeks later. The small percentage of patients who continue to be infected with *C. diphtheriae* after treatment should receive an additional 10-day course of oral erythromycin or rifampin. Plasmid-mediated resistance to erythromycin of the MLS type emerged transiently in *C. diphtheriae* during the Seattle epidemic, but its frequency declined dramatically after the routine use of erythromycin was discontinued.

Patients with respiratory or cutaneous diphtheria caused by *tox*+ *C. diphtheriae* or by strains of unknown toxinogenicity should be hospitalized, kept in bed initially, handled with isolation procedures appropriate for the site of infection, and given supportive care as needed. Respiratory and cardiac function must be monitored closely. Early intubation

or tracheostomy is recommended when the larynx is involved or signs of impending airway obstruction are detected. Tracheobronchial membrane can sometimes be removed mechanically via the endotracheal tube or tracheostomy. Primary or secondary pneumonia should be diagnosed and treated promptly. Sedative or hypnotic drugs that may mask respiratory symptoms are contraindicated. Close electrocardiographic monitoring, treatment of arrhythmias, and electrical pacing for heart block are essential. Congestive heart failure should be treated as described in Chap. 232. Glucocorticoids do not reduce the risk of diphtheritic myocarditis or polyneuritis. Ulcerative or ecthymatous cutaneous lesions should be treated with Burow's solution applied on wet compresses after debridement of necrotic areas, and treatment for associated conditions such as pediculosis, scabies, or underlying dermatoses should be instituted. Recovery from diphtheria does not always confer active immunity, and initiation of an immunization regimen for diphtheria that is appropriate for the patient's age should be an integral part of the treatment plan.

### PREVENTION

Vaccines available in the United States for immunization against diphtheria include diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP), diphtheria and tetanus toxoids adsorbed (DT; for pediatric use), and tetanus and diphtheria toxoids adsorbed (Td; for adult use). DTaP is preferred over DTP for primary immunization of children without contraindications, and use of DTP is no longer recommended. Td contains less diphtheria toxoid than DTP, DTaP, or DT and causes fewer adverse reactions in adults. Current guidelines for primary immunization of children and adults against diphtheria and for maintaining immunity by periodic booster doses of appropriate vaccines throughout life are summarized in Chap. 122.

Close contacts of diphtheria patients should be cultured for *C. diphtheriae*, kept under surveillance for 1 week, and treated with appropriate antibiotics if cultures are positive. Previously immunized close contacts should receive an appropriate booster containing diphtheria toxoid if their last booster was given>5 years previously. If immunization status is uncertain, close contacts should receive an antibiotic regimen appropriate for carriers and a primary immunization series appropriate for their age.

## OTHER CORYNEBACTERIAL INFECTIONS

### DEFINITION

Medically important coryneform bacteria (formerly called *diphtheroids*) include members of the normal flora that cause opportunistic infections, human pathogens of relatively low virulence, and animal pathogens that cause occasional zoonotic infections. Reported infections caused by coryneform bacteria have increased substantially in number over the past two decades. Isolates of *C. jeikeium* and *C. urealyticum* are often resistant to multiple antibiotics.

### ETIOLOGY AND LABORATORY DIAGNOSIS

Because coryneform bacteria are potential pathogens, it is important not to dismiss

them as constituents of the normal flora or as contaminants when they are found in clinical specimens. Laboratory differentiation of coryneform bacteria is important when they are isolated repeatedly, when they are recovered in pure culture or in large numbers, or when they form pigmented or hemolytic colonies.

The coryneform bacteria are a large, heterogeneous group of gram-positive, pleomorphic, irregularly staining bacilli or coccobacilli that superficially resemble *C. diphtheriae* and are difficult to identify and classify. The genus *Corynebacterium* is currently divided into three groups of species: the nonlipophilic, fermentative corynebacteria (including *C. diphtheriae*, *C. xerosis*, *C. striatum*, *C. minutissimum*, and others); the nonlipophilic, nonfermentative corynebacteria (including *C. pseudodiphtheriticum* and others); and the lipophilic corynebacteria (including *C. jeikeium*, *C. urealyticum*, and others). Coryneform bacteria also belong to many other genera (including *Actinomyces*, *Arcanobacterium*, and *Rhodococcus*) as well as to several groups that have not yet been assigned to genera and species by the U.S. Centers for Disease Control and Prevention (CDC).

## ECOLOGY AND EPIDEMIOLOGY

Humans are the probable natural reservoir for *C. xerosis*, *C. pseudodiphtheriticum* (formerly *C. hofmannii*), *C. striatum*, *C. minutissimum*, *C. jeikeium* (formerlyCDCgroup JK), *C. urealyticum* (formerly CDC group D2), and *Arcanobacterium haemolyticum* (formerly *C. haemolyticum*). Animals are the probable natural reservoir for *Actinomyces pyogenes* (formerly *C. pyogenes*; cows, sheep, pigs), *C. ulcerans* (cows, horses), and *C. pseudotuberculosis* (sheep, horses, goats, cattle). The natural reservoir for *Rhodococcus equi* (formerly *C. equi*) is soil. The ecologic niches for many other coryneform bacteria of medical importance are not well defined.

The coryneform bacteria found most frequently as components of the normal flora include *C. pseudodiphtheriticum* (pharynx, skin), *C. xerosis* (conjunctival sac, nasopharynx, skin), and *C. striatum* (anterior nares, skin). Coryneform bacteria that commonly colonize the skin of hospitalized patients include *C. jeikeium* (axilla, groin, perineum) and *C. urealyticum*. *C. jeikeium* most often colonizes patients with malignancies or severe immunodeficiency; it is also isolated from environmental sources (surfaces, air) in hospitals and from the hands of ward staff. *C. ulcerans* infections are acquired by consumption of raw milk. *C. pseudotuberculosis* infections are acquired by contact with animals or animal products or by consumption of raw milk.

## PATHOGENESIS AND CLINICAL MANIFESTATIONS

*C. jeikeium* was recognized in 1976 as a cause of infections in immunocompromised hosts. This organism also causes infections in immunocompetent hosts, but severe infections continue to be most frequent in patients with hematologic malignancies and neutropenia. Skin colonization precedes clinical infection. Additional risk factors for nosocomial *C. jeikeium* sepsis include prolonged hospitalization, breaks in the integument, chronic intravascular catheterization, and prior treatment with broad-spectrum antibiotics. Other presentations of *C. jeikeium* infection include endocarditis, device-related infections, pulmonary infiltrates, cutaneous septic emboli, soft tissue infections, and rashes. Endocarditis due to *C. jeikeium* occurs primarily in

patients with prosthetic heart valves. *C. jeikeium* is a rare cause of central nervous system infections in patients with ventricular shunts.

*C. urealyticum* (formerlyCDCgroup D2) was identified in 1985 as a significant cause of nosocomial urinary tract infections, including acute and chronic cystitis and pyelonephritis. The organism closely resembles *C. jeikeium* but differs from the latter by producing urease and failing to convert glucose to acidic metabolites. Hydrolysis of urea by urease causes alkalinization of the urine and formation of ammonium magnesium phosphate (struvite) stones. *C. urealyticum* is a cause of alkaline-encrusted cystitis in patients with preexisting bladder lesions that serve as foci for precipitation of struvite crystals. Risk factors associated with symptomatic urinary tract infections include preexisting immunosuppression, recent urologic procedures (including renal transplantation), underlying disorders of the genitourinary tract, and a history of urinary tract infections.

*A. haemolyticum* causes pharyngitis and chronic skin ulcers; less frequently, it causes a variety of deep tissue infections, septicemia, and endocarditis. Some 90% of *A. haemolyticum* infections occur in patients between 10 and 30 years old. *A. haemolyticum* pharyngitis in this age group is 5 to 13% as frequent as *Streptococcus pyogenes* pharyngitis. An erythematous rash is present in 30 to 67% of cases. The rash is usually scarlatiniform and most pronounced on the trunk and proximal extremities, but it sometimes resembles urticaria or erythema multiforme. Because rash is more frequent in *A. haemolyticum* infections than in *S. pyogenes* infections, *A. haemolyticum* should be considered as a possible etiology in older children and adults who present with the scarlet fever syndrome. Infection due to *A. haemolyticum* can also present as extensive pharyngeal exudate and can mimic diphtheria. *A. haemolyticum* occasionally causes peritonsillar abscess, sepsis, endocarditis, or meningitis.

*C. minutissimum* is frequently isolated from the lesions of erythrasma (Fig. 141-CD2), a common superficial skin infection characterized by the presence in intertriginous areas of reddish-brown, scaly, pruritic, macular patches that exhibit coral-red fluorescence under a Wood's light. The etiology of erythrasma appears to be polymicrobial; infection of the skin by *C. minutissimum* has been shown to follow the onset of maceration and scaling. Deep infections caused by *C. minutissimum* are rare and include abscesses, bacteremia, endocarditis, peritonitis, pyelonephritis, and infection of central venous catheters.

Among coryneform bacteria that cause disease in animals and occasionally in humans, *R. equi* has emerged as an important intracellular opportunistic pathogen in immunocompromised patients. Most reported cases are necrotizing pulmonary infections that resemble tuberculosis or nocardiosis in patients with severely defective cell-mediated immunity. Cases of *R. equi* infection are being diagnosed with increasing frequency in patients with AIDS.

*A. pyogenes* causes bovine mastitis, a disease transmitted by flies. Yearly epidemics of leg ulcers infected with *A. pyogenes* occurred among schoolchildren in Thailand between 1979 and 1984 and were postulated to have resulted from introduction of the organism into traumatic skin lesions by flies. Reported *A. pyogenes* infections in adults in Denmark have included abscesses, cystitis, intraabdominal infections, and mastoiditis

with bacteremia.

*C. ulcerans* infections in humans usually present as pharyngitis and can mimic respiratory diphtheria, whereas infections caused by *C. pseudotuberculosis* typically present as suppurative granulomatous lymphadenitis. Some strains of *C. ulcerans* and *C. pseudotuberculosis* produce diphtheria toxin. Human infections by *tox*+ strains of *C. ulcerans* -- but not by *tox*+ strains of *C. pseudotuberculosis* -- have been reported, and administration of diphtheria antitoxin is therefore warranted in infections by *C. ulcerans* that are presumed on clinical grounds to be caused by toxinogenic strains.

*C. pseudodiphtheriticum*, a commensal of low virulence, is an uncommon cause of pneumonia in men with AIDS and of endocarditis, necrotizing tracheitis, tracheobronchitis, and urinary tract infection in patients without known immune deficiencies. Likewise, *C. xerosis* and *C. striatum* only occasionally cause human infections.

## DIAGNOSIS

The clinical features of *C. jeikeium* infections are not pathognomonic. The diagnosis of these infections is based on a high index of suspicion, identification of the organism by culture in appropriate clinical specimens, and exclusion of other likely causes of infection.

*C. urealyticum* often goes undetected by routine urine cultures; rather, it is necessary to incubate the cultures for 24 to 48 h on blood agar or on special media. Cultivation should be prolonged in selected cases -- i.e., those involving patients (especially elderly men with preexisting genitourinary abnormalities) with alkaline urine, ammonium magnesium phosphate stones, gram-positive bacilli in the urine, or negative standard urine cultures despite clinical evidence of bacteriuria. Other microbes that can cause urinary tract infections with alkaline urine include *Proteus*, *Ureaplasma*, and some staphylococci and streptococci. Alkaline-encrusted cystitis is an anatomic diagnosis made by cystoscopy.

The differential diagnosis of *A. haemolyticum* pharyngitis with rash includes scarlet fever; rubella; staphylococcal and streptococcal toxic shock syndromes; infections caused by Epstein-Barr virus, cytomegalovirus, and enteroviruses (especially coxsackieviruses); disseminated gonococcal infection; secondary syphilis; and drug allergy. Routine diagnostic methods for throat cultures are not ideal for the detection of *A. haemolyticum*, nor is this organism detected by the rapid tests for *S. pyogenes* that are sometimes substituted for throat cultures. Pharyngitis caused by *A. haemolyticum* in adolescents and adults is likely to be underdiagnosed until improved tests for the organism are used by diagnostic laboratories.

Erythrasma is diagnosed clinically. Because of uncertainty about the etiologic role of *C. minutissimum*, culture of erythrasma lesions is not currently recommended. Pharyngitis caused by *tox*+ strains of *C. ulcerans* may be clinically indistinguishable from diphtheria. The presentations of infections caused by other coryneform bacteria are not usually diagnostic; cultures are required for identification of the causal organisms.

## TREATMENT

Strains of *C. jeikeium* are typically resistant to most antibiotics. Vancomycin is the drug of choice for empirical treatment of infections caused by this organism, although antimicrobial susceptibility testing may reveal other antibiotic options for some isolates. For device-related *C. jeikeium* infections, removal of the infected device is usually required in addition to appropriate antibiotic therapy.

*C. urealyticum* is often resistant to the antibiotics used commonly for the treatment of urinary tract infections. Empirical treatment with vancomycin is appropriate pending the results of antimicrobial susceptibility testing. Several courses of antibiotic therapy may be necessary for bacteriologic cure. Patients with alkaline-encrusted cystitis require resection of the encrusted lesions in addition to antibiotic therapy.

No controlled trials of treatment for *A. haemolyticum* infections have been performed. In vitro tests usually demonstrate susceptibility to penicillins, erythromycin, azithromycin, clindamycin, doxycycline, ciprofloxacin, and vancomycin, but treatment failures have been reported with appropriate doses of penicillins. Limited data suggest that the clinical course of *A. haemolyticum* pharyngitis may be shortened by treatment with erythromycin.

Infections with *C. ulcerans* that present like diphtheria or are known to be caused by *tox*+ strains should be treated like diphtheria. Oral erythromycin is usually effective for treatment of erythrasma. For infections caused by *R. equi*, vancomycin is the drug of choice. Possible alternatives include erythromycin, rifampin, aminoglycosides, and chloramphenicol; the combination of erythromycin and rifampin is attractive because of possible synergy. Penicillins should not be used, because *R. equi* rapidly develops resistance. Many weeks of antibiotic treatment, sometimes supplemented by surgical intervention, are often needed for infections caused by *R. equi*. Suppressive therapy with antibiotics should be continued indefinitely in patients with AIDS after initial treatment of infections caused by *R. equi*. Initial treatment of infections caused by other coryneform bacteria should be based on the identity of the organism and published data regarding antibiotic susceptibility. Therapy should be modified, when necessary, in light of the results of antibiotic susceptibility tests.

# ANTHRAX

## DEFINITION

Anthrax is an infection caused by *Bacillus anthracis* that occurs primarily in herbivores. Humans become infected when *B. anthracis* spores are introduced into the body by contact with infected animals or contaminated animal products, insect bites, ingestion, or inhalation. Aerosolized spores of *B. anthracis* have the potential for use in biological warfare or bioterrorism. Cutaneous anthrax is most common and is characterized by the development of a localized skin lesion with a central eschar surrounded by marked nonpitting edema. Inhalation anthrax (woolsorters' disease) typically involves hemorrhagic mediastinitis, rapidly progressive systemic infection, and a very high mortality rate. Gastrointestinal anthrax is rare and is associated with a high mortality rate.

## ETIOLOGIC AGENT AND EPIDEMIOLOGY

*B. anthracis* is a large, aerobic, spore-forming, gram-positive rod that is encapsulated and nonmotile and grows in chains. Sporulation does not take place in living animals. The rectangular shape of the individual bacteria gives chains of *B. anthracis* a boxcar-like appearance. Virulent strains of *B. anthracis* are pathogenic for animals, including mice and guinea pigs. Spores of *B. anthracis* can survive for years in dry earth but are destroyed by boiling for 10 min, by treatment with oxidizing agents such as potassium permanganate or hydrogen peroxide, or by dilute formaldehyde. Most strains of *B. anthracis* are susceptible to penicillin.

Anthrax occurs worldwide and is most prevalent among domestic herbivores (including cattle, sheep, horses, and goats) and wild herbivores. Grazing animals become infected when they forage for food in areas contaminated with spores of *B. anthracis*. Anthrax in herbivores tends to be severe, with high mortality. Terminally ill animals with overwhelming bacteremic infections often bleed from the nose, mouth, and bowel, thereby contaminating soil or water with vegetative *B. anthracis* that can sporulate and persist in the environment. The carcasses of infected animals provide additional potential foci of contamination.

Humans are more resistant to anthrax than are herbivorous animals. The estimated number of human cases worldwide is 20,000 to 100,000 per year. Human cases are classified as agricultural or industrial. Agricultural cases result most often from contact with animals that have anthrax (e.g., during skinning, butchering, or dissecting), from bites of contaminated or infected flies, and (in rare instances) from consumption of contaminated meat. Industrial cases are associated with exposure to contaminated hides, goat hair, wool, or bones. Only three cases of cutaneous anthrax were reported to theCDC from 1984 through 1993, and gastrointestinal anthrax has never been documented in the United States. In an epidemic in the former Soviet Union at Sverdlovsk in 1979, cases were initially reported as cutaneous and gastrointestinal anthrax associated with contaminated meat; however, subsequent analysis of epidemiologic data and autopsy findings for most of the fatal cases established that the disease was inhalational anthrax associated with accidental airborne release of *B. anthracis* from a nearby military biological weapons facility. A massive outbreak in Zimbabwe between 1978 and the early 1980s involved more than 9700 cases of agricultural anthrax in humans. This outbreak occurred during wartime and was associated with disruption of the veterinary and medical infrastructure and cessation of veterinary anthrax vaccination programs.

## PATHOGENESIS

*B. anthracis* can evade phagocytosis, invade the bloodstream, multiply rapidly to a high population density in vivo, and kill quickly. The poly-D-glutamic acid capsule of *B. anthracis* confers resistance to phagocytosis. Anthrax toxin consists of three different proteins called *protective antigen* (PA), *edema factor* (EF), and *lethal factor* (LF). The toxin was discovered in studies demonstrating that transfer of sterile blood from guinea pigs dying of anthrax to uninfected guinea pigs killed the recipients. PA binds to plasma membranes of target cells and is cleaved by a cellular protease into two fragments. The

larger fragment remains on the cell surface, displays a binding site for a domain that is present in both EF and LF, and serves as a specific receptor that mediates endocytic entry of EF or LF into the target cells. The catalytic activity of EF, a calmodulin-dependent adenylate cyclase, is expressed in the cytoplasm of human or animal cells that contain both calmodulin and ATP. The biologic effects of EF, which include formation of edema in anthrax lesions and inhibition of polymorphonuclear leukocyte functions, are mediated by the intracellular cyclic AMP that is produced by the enzymatic action of EF. In contrast, LF is a highly specific endopeptidase that cleaves several members of the MAP-kinase-kinase protein family and inactivates their functions in signal transduction pathways. Macrophages appear to be the principal targets of LF in animals, and intoxication of macrophages by LF is associated with production of reactive oxygen species, release of cytokines (including tumor necrosis factor a and interleukin 1b), shock, and death.

Cutaneous anthrax is initiated when spores of *B. anthracis* are introduced into the skin through cuts or abrasions or by biting flies. The spores germinate within hours, and the vegetative cells multiply and produce anthrax toxin. The cutaneous anthrax lesion is characterized by necrosis, vascular congestion, hemorrhage, and gelatinous edema, but few leukocytes are present.

In inhalational anthrax, *B. anthracis* spores in airborne particles <5 um in diameter are deposited directly into the alveoli or alveolar ducts. The spores are phagocytized by alveolar macrophages, and some are carried to and germinate in mediastinal nodes. Hemorrhagic necrosis of the nodes, associated with hemorrhagic mediastinitis and overwhelming *B. anthracis* bacteremia, may develop rapidly. Secondary pneumonia sometimes occurs.

Gastrointestinal anthrax usually results from ingestion of inadequately cooked meat from animals with anthrax. Primary infection can be initiated in the intestine by organisms that survive passage through the stomach. An oropharyngeal form of the disease has also been described. Lesions in the throat or intestine are usually accompanied by hemorrhagic lymphadenitis.

*B. anthracis* bacteremia occurs in almost all cases of anthrax that progress to a fatal outcome.

## CLINICAL MANIFESTATIONS

Approximately 95% of human cases of anthrax are the cutaneous form, and ~5% are the inhalational form. Gastrointestinal anthrax is very rare. Anthrax meningitis can occur as a complication of overwhelming *B. anthracis* bacteremia.

**Cutaneous Anthrax** The cutaneous lesion in anthrax is most often found on exposed areas of skin. A small red macule develops within days after inoculation of *B. anthracis* spores into skin. During the next week, the lesion typically progresses through papular and vesicular or pustular stages to the formation of an ulcer with a blackened necrotic eschar surrounded by a highly characteristic expanding zone of brawny edema. The early lesion may be pruritic, and the fully developed lesion is painless. Small satellite vesicles may surround the original lesion, and painful nonspecific regional lymphadenitis

is common. Most patients are afebrile, with mild or no constitutional symptoms; in severe cases, edema may be extensive and associated with shock. Spontaneous healing occurs in 80 to 90% of untreated cases, but edema may persist for weeks. In the 10 to 20% of untreated patients who have progressive infection, bacteremia develops and is often associated with high fever and rapid death. The differential diagnosis includes staphylococcal skin infections, tularemia, plague, and orf. Cutaneous anthrax should be considered when patients have painless ulcers associated with vesicles and edema and have had contact with animals or animal products.

**Inhalational Anthrax** The presenting symptoms of inhalational anthrax (woolsorters' disease) resemble those of severe viral respiratory diseases. Early diagnosis of inhalational anthrax that occurs naturally or as a consequence of biological warfare or bioterrorism is difficult. After 1 to 3 days, an acute phase supervenes, with increasing fever, dyspnea, stridor, hypoxia, and hypotension usually leading to death within 24 h. Occasionally, patients present with fulminant disease. A characteristic radiologic finding associated with hemorrhagic mediastinitis is symmetric mediastinal widening, which may provide an early clue to the diagnosis of inhalational anthrax.

**Gastrointestinal Anthrax** Symptoms of gastrointestinal anthrax are variable and include fever, nausea and vomiting, abdominal pain, bloody diarrhea, and sometimes rapidly developing ascites. Diarrhea is occasionally massive in volume. The major features of oropharyngeal anthrax are fever, sore throat, dysphagia, painful regional lymphadenopathy, and toxemia; respiratory distress may be evident. The primary lesion is most often located on the tonsils.

## LABORATORY DIAGNOSIS

*B. anthracis* is present in large numbers in cutaneous lesions of anthrax and can be demonstrated by Gram's staining, direct fluorescent antibody staining, or culture unless the patient has been treated with antibiotics. A small proportion of patients with anthrax have bacteremia. Patients with anthrax meningitis have bloody spinal fluid containing large numbers of *B. anthracis* demonstrable by staining or culture. Patients with mild disease usually have normal leukocyte counts, but those with disseminated disease typically have polymorphonuclear leukocytosis. Tests for antibody to *B. anthracis* are useful in confirming the diagnosis of anthrax.

## TREATMENT

Viable *B. anthracis* disappears from the lesions of cutaneous anthrax within 5 h of the initiation of treatment with parenteral penicillin G. The recommended regimen for adults is 2 million units of penicillin G at intervals of 6 h until edema subsides, with the subsequent administration of oral penicillin to complete a 7- to 10-day course. For penicillin-sensitive adults, treatment with ciprofloxacin, erythromycin, tetracycline, or chloramphenicol can be substituted. Antibiotics decrease local edema and systemic toxicity in cutaneous anthrax but do not prevent eschar formation. Cutaneous lesions should be cleaned and covered, and used dressings should be decontaminated. For inhalational or gastrointestinal anthrax, high-dose penicillin (8 to 12 million units per day in divided doses at intervals of 4 to 6 h) is recommended. A rational case can be made for passive immunization with anthrax antitoxin in addition to antibiotic therapy in

severely ill patients with anthrax, but no appropriate antitoxin is commercially available.

## PREVENTION

Inhalational anthrax was essentially eliminated in England before 1940 through the development of methods to decontaminate wool and goat hair and the improvement of working conditions for handlers of animal products.

Nonliving vaccines consisting of alum-precipitated or aluminum hydroxide-adsorbed extracellular components of unencapsulated *B. anthracis* are used in the United States for military personnel, agricultural workers, veterinary personnel, and others at risk of exposure to anthrax. The major active component of these vaccines is protective antigen. Live attenuated vaccines containing spores of *B. anthracis* are used in both developed and developing countries to immunize domestic herbivores; these preparations are also used to immunize humans in Russia but not in the United States. The probable basis for attenuation of the original Pasteur spore vaccine is partial loss of a plasmid that encodes anthrax toxin. The basis for attenuation of the current Sterne spore vaccine is loss of a plasmid that encodes capsular polypeptide.

Improved anthrax vaccines for humans are needed because the current vaccines are impure and chemically complex, elicit only slow onset of protective immunity, provide incomplete protection, and cause significant adverse reactions. In addition to agricultural and industrial anthrax, the possible use of *B. anthracis* as an agent of biological warfare or bioterrorism is a stimulus for the development of an improved vaccine. Current strategies for vaccine development include purification of candidate protective antigens, expression of protective antigens in recombinant microbial vaccines, and construction of improved live attenuated strains of *B. anthracis*.

Carcasses of animals that succumb to anthrax should be buried intact or cremated. Necropsy or butchering of infected animals should be avoided because sporulation of *B. anthracis* occurs only in the presence of oxygen.

## PROGNOSIS

The mortality rate is 10 to 20% for untreated cutaneous anthrax but is very low with appropriate antibiotic therapy. In contrast, the mortality rate for inhalational anthrax approaches 100%, and therapy is usually unsuccessful. The mortality rate in treated gastrointestinal anthrax is ~50%. Anthrax meningitis is usually fatal.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 142. INFECTIONS CAUSED BY *LISTERIA MONOCYTOGENES* - *Anne Schuchat*, *Claire V. Broome*

*Listeria monocytogenes* is a gram-positive rod that can be isolated from soil, vegetation, and many animal reservoirs. Human disease due to *L. monocytogenes* generally occurs in the setting of pregnancy or of immunosuppression caused by illness or medication. Increasing evidence suggests that a substantial portion of cases of human listeriosis are attributable to the food-borne transmission of *L. monocytogenes*. Unlike most food-borne pathogens, which cause primarily gastrointestinal illness, *L. monocytogenes* causes invasive syndromes, such as meningitis, sepsis, chorioamnionitis, and stillbirth.

### ETIOLOGY

Listeriae are aerobic or facultatively anaerobic nonsporulating bacilli that grow at 1 to 45°C and typically have tumbling motility when cultured at 20 to 25°C. Characteristics that help distinguish *L. monocytogenes* from other *Listeria* spp. include the formation of a narrow zone of b hemolysis on sheep blood agar and the production of acid from glucose, maltose, L-rhamnose, anda-methyl-D-mannoside but not from D-xylose. Determination of the serotype of *L. monocytogenes* is based on somatic (O) and flagellar (H) antigens. Most cases of human disease are caused by serotypes 1/2a, 1/2b, and 4b. Molecular subtyping techniques have made it easier to discriminate among strains of *Listeria* and thus to link environmental or food isolates with clinical infections.

### PATHOGENESIS

*L. monocytogenes* is an intracellular pathogen -- a characteristic consistent with its predilection for causing illness in persons with deficient cell-mediated immunity. The organism can be found as part of the gastrointestinal flora in healthy individuals. Lack of gastric acidity and abnormal gastrointestinal functioning may increase the risk of invasive disease following exposure to the organism in the gastrointestinal tract. The increased risk of *L. monocytogenes* infection in pregnant women may be due to both systemic and local immunologic changes associated with pregnancy. For example, local immunosuppression at the maternal-fetal interface of the placenta may facilitate intrauterine infection following transient maternal bacteremia.

The molecular pathogenesis of *L. monocytogenes* has recently been elucidated. The cell-surface protein internalin interacts with specific receptors to induce phagocytosis. Both listeriolysin O and phospholipases permit the organism to escape from the phagosome into the cytosol while avoiding intracellular killing. Through the surface protein Act A, *L. monocytogenes* uses actin-based motility to move to the cell membrane. Efficient cell-to-cell spread is accomplished by both actin filament formation and phospholipase production. Genetic determinants of these proteins have been characterized. Because the organism is adapted for both intracellular survival and direct cell-to-cell spread, it is not eliminated by antibodies.

### EPIDEMIOLOGY

Long recognized as a veterinary pathogen, *L. monocytogenes* causes basilar meningitis

("circling disease") and stillbirth in sheep and cattle. The occurrence of listeriosis among humans has received increasing attention as the role of contaminated foods in the pathogenesis of epidemic listeriosis has been recognized and reports of disease associated with the expanding immunosuppressed population have accumulated.

Invasive listeriosis -- confirmed by culture of blood or cerebrospinal fluid (CSF) -- occurs in approximately 5 individuals per million population annually in the United States, for an estimated 1400 cases per year. Perinatal listeriosis complicates 9 births per 100,000. A 40% decline in incidence since the period from 1986 through 1990 may be attributable to aggressive food regulation and industrial clean-up efforts. Multistate surveillance for sporadic listeriosis suggests that 20% of infections are fatal or result in stillbirth, although higher case-fatality rates have been reported during listeriosis epidemics and were described in early series. Most cases of disease due to *L. monocytogenes* are sporadic; however, investigation of several outbreaks of listeriosis during the 1980s and 1990s demonstrated common-source food-borne transmission as a cause of human illness and showed that the incubation period for disease following consumption of contaminated food can be 2 to 6 weeks. The largest North American outbreak, which took place in Los Angeles in 1985, involved more than 100 cases and 48 deaths or stillbirths. A nationwide outbreak in France in 1992 involved 279 cases and 63 deaths. Foods implicated in outbreaks of listeriosis include contaminated coleslaw, pasteurized milk, soft cheeses, pate, ready-to-eat pork products, and hot dogs, while epidemiologic studies have implicated undercooked chicken, uncooked hot dogs, soft cheeses, and food from store delicatessen counters in sporadic disease. Listerial contamination of foods is relatively common. Among foods contaminated with the organism, those that are purchased ready to eat, are contaminated with serotype 4b, and are contaminated at a relatively high level may be the most likely to cause illness. The long incubation period associated with listeriosis contributes to the difficulty of implicating specific foods as the cause of either common-source outbreaks or sporadic cases.

Although food-borne transmission appears to be the foremost cause of epidemic and sporadic disease, several clusters of late-onset neonatal infection suggest nosocomial transmission of *L. monocytogenes*. Contaminated multiuse materials and equipment have been suggested as causes of some nosocomial clusters. Listeriosis has been reported in veterinarians and other persons in close contact with infected animals.

## CLINICAL PRESENTATION

*Pregnancy-associated listeriosis* may occur during any stage of pregnancy, although most infections are detected during the third trimester, possibly because of failure to obtain specimens for bacterial culture earlier during gestation in instances of abortion and stillbirth. One-half to two-thirds of pregnant women with perinatal listeriosis experience a mild illness characterized by fever, myalgias, malaise, and backache, which sometimes are accompanied by diarrhea, abdominal pain, nausea, and/or vomiting during the bacteremic phase. Blood cultures should be used for diagnosis. Transplacental spread of the organism results in intrauterine infection, which can lead to chorioamnionitis, premature labor, intrauterine fetal demise, or early-onset disease of the newborn. Women with listeriosis diagnosed during pregnancy have a favorable clinical outcome after antibiotic therapy or delivery. Although often included in the differential diagnosis of recurrent spontaneous abortion, infection with *L.*

*monocytogenes* appears to cause fewer than 2% of stillbirths.

*Neonatal listeriosis* can be classified under the same categories used for group B streptococcal infection (Chap. 140), with early-onset disease evident during the first week of life and late-onset disease developing thereafter. Infants may be symptomatic at birth; most infants with early-onset disease are symptomatic by the second day of life. Aspiration of infected amniotic fluid contributes to pathogenesis. Early-onset disease may include sepsis, respiratory distress, skin lesions, and the syndrome called *granulomatosis infantisepticum*, which is characterized by disseminated abscesses involving the liver, spleen, adrenal glands, lungs, and other sites. Infants with late-onset neonatal disease are more likely than those with early-onset disease to develop meningitis. While early-onset disease is often associated with obstetric complications such as premature delivery and chorioamnionitis, late-onset disease typically affects infants born at term by uncomplicated deliveries. Infants may acquire *L. monocytogenes* during passage through the birth canal; except in several clusters of late-onset neonatal infections linked to nosocomial transmission, the pathogenesis of late-onset disease is not well understood.

*Listeriosis not associated with pregnancy* usually affects persons with immunosuppressive conditions, although invasive disease can also affect immunocompetent adults, particularly elderly persons. The most common underlying conditions in nonpregnant adults with listeriosis are chronic glucocorticoid therapy, solid or hematologic malignancies, diabetes mellitus, renal disease, liver disease, and AIDS. Although the prevalence of listeriosis among persons infected with HIV is much higher than that in the general population, listeriosis is a relatively uncommon opportunistic infection in AIDS.

**Sepsis** Clinical studies have shown that bacteremic infection without an evident focus is the most common clinical manifestation of listeriosis among immunocompromised hosts, while infection of the central nervous system (CNS) ranks second in frequency. Listerial sepsis cannot be distinguished clinically from bacteremia involving other organisms. Patients are usually febrile, often appear extremely ill, and may have prodromal symptoms including myalgia, nausea, vomiting, and diarrhea. Immunocompromised patients with listeriosis are less likely than other adults to present with CNS infection, possibly because they are more likely to have blood cultured during febrile episodes and thus to have transient listerial bacteremia recognized.

**CNS Infection** The most common presentation ofCNSinfection due to *L. monocytogenes* is meningitis, which can present as either an acute or (less often) a subacute illness. Presenting symptoms include fever, headache, and an altered level of consciousness. Examination ofCSFusually reveals pleocytosis, increased protein concentrations, and normal glucose levels, although other patterns are sometimes found. Gram's stain is often unrevealing. The diagnosis is made when *L. monocytogenes* is identified on culture. Despite its name, *L. monocytogenes* is rarely associated with monocytosis of either CSF or blood. Other syndromes seen in CNS infection include meningoencephalitis; cerebritis; and brainstem, spinal cord, or intracranial abscesses. The unusual syndrome of rhombencephalitis includes asymmetric cranial-nerve palsies, altered consciousness, cerebellar signs, and motor or sensory loss. Symptoms of other nonmeningitic CNS infections include fever, ataxia,

seizures, personality changes, and coma. Nuchal rigidity is rare in nonmeningitic infections. CSF cultures may be sterile; blood cultures are usually diagnostic.

**Endocarditis** Like most forms of bacterial endocarditis, listerial endocarditis typically occurs in patients with prosthetic or previously damaged valves. The organism has a predilection for the left side of the heart. Endocarditis due to *L. monocytogenes* is often associated with systemic embolization.

**Focal Infections** Other focal infections that can follow unrecognized bacteremia include endophthalmitis, peritonitis, osteomyelitis, visceral abscess, pleuropulmonary infection, and cholecystitis. Cutaneous lesions may develop without systemic involvement and have been reported in veterinarians and poultry workers.

**Recurrences** Recurrent infection with *L. monocytogenes* has been reported but is rare. Many recurrences are due to the subtype responsible for the initial infection. The implication is that such recurrences result either from insufficient treatment of a focus of primary infection or from repeated exposure to a persistently contaminated source.

**Gastrointestinal Illness** Several common-source outbreaks of acute gastroenteritis suggest that *L. monocytogenes* can cause an acute diarrheal syndrome in persons without immunocompromising conditions. The importance of *L. monocytogenes* in sporadic diarrheal illness is unclear. Although the organism is not identified by the culture methods routinely used for stool specimens, studies using selective enrichment media for evaluation of consecutive specimens from patients hospitalized with acute diarrhea have suggested that *L. monocytogenes* is not a major cause of sporadic diarrhea.

## DIAGNOSIS

Invasive listeriosis is diagnosed when the organism is cultured from a site that is usually sterile, such as blood,CSF, or amniotic fluid. The organism grows readily within 36 h on routine culture media, but morphologic similarities between *Listeria* and both diphtheroids and streptococci make it necessary to use biochemical tests to identify the species. Serologic assays with whole-cell antigens have not been useful for the diagnosis of listeriosis, both because exposure to the organism (and thus the presence of antibody) may be common and because infected individuals may not produce antibody. Assays for antibody to listeriolysin O have been applied in epidemiologic investigations and, retrospectively, in the diagnosis of culture-negativeCNSinfection. Culture of the organism from nonsterile sites such as the vagina and rectum is not useful for clinical diagnosis, as the organism may be carried at these sites by approximately 5% of healthy individuals.

*Differential diagnosis* of prematurity, spontaneous abortion, or stillbirth includes infectious diseases such as group B streptococcal infection, congenital syphilis, and toxoplasmosis; pathogens such as group B streptococci and *Escherichia coli* are more common than *L. monocytogenes* as causes of meningitis and sepsis in the newborn period. Listerial infection should always be considered in the differential diagnosis of meningitis in immunosuppressed persons, particularly transplant recipients and others undergoing glucocorticoid treatment, patients with hematologic malignancy, and

HIV-infected patients. Among healthy adults, meningitis is much more likely to be caused by *Neisseria meningitidis*, *Streptococcus pneumoniae*, or viral pathogens than by *L. monocytogenes*.

## TREATMENT

The treatment of choice for listeriosis is intravenous administration of either ampicillin or penicillin, often in combination with an aminoglycoside for synergy. Trimethoprim-sulfamethoxazole is bactericidal against *L. monocytogenes* and has been used successfully in the treatment of patients with penicillin allergy. *L. monocytogenes* is susceptible in vitro to penicillin G, ampicillin, erythromycin, trimethoprim-sulfamethoxazole, chloramphenicol, rifampin, tetracyclines, aminoglycosides, and imipenem. However, chloramphenicol and rifampin may antagonize the bactericidal effect of penicillins. Because *L. monocytogenes* is not sensitive to cephalosporins, these agents should not be used for single-agent empirical treatment of neonatal sepsis or of meningitis in newborns or immunocompromised hosts.

Dosages and durations of therapy have not been subjected to controlled trials. For nonpregnant adults with listeriosis, the regimen of choice is either ampicillin (12 g intravenously per day in six divided doses) or penicillin G (15 to 20 million units intravenously per day in six divided doses); for immunosuppressed patients with meningitis, some experts add gentamicin (1.3 mg/kg intravenously every 8 h) for synergy. Penicillin-allergic patients may be treated with trimethoprim-sulfamethoxazole (15/75 mg/kg intravenously per day in three equal portions every 8 h). Meningitis in an immunocompetent patient may require 2 to 3 weeks of antibiotic therapy after defervescence. Meningitis, bacteremia, endocarditis, and nonmeningitic listeriosis in immunosuppressed patients should be treated longer, probably for 4 to 6 weeks. Neonatal listeriosis can be treated with a 2-week course of ampicillin. Infants weighing <2000 g should receive 100 mg/kg per day in two equal doses during the first week of life and 150 mg/kg per day during the second week. Infants weighing³2000 g should receive 150 mg/kg per day in three equal doses during the first week of life and 200 mg/kg per day during the second week. The addition of an aminoglycoside should be considered for neonatal infection (gentamicin, 5 mg/kg per day in two divided doses during the first week of life; 7.5 mg/kg per day in three equal doses during the second week). For listeriosis in pregnant women, a 2-week course of ampicillin (4 to 6 g per day in four equal doses) is recommended. During the last month of pregnancy, infected women with serious penicillin allergies may be treated with erythromycin.

## PROGNOSIS

Treatment of maternal bacteremia during pregnancy can prevent neonatal infection. Antibiotic therapy for the newborn can limit sequelae, although the widely disseminated disease characteristic of granulomatosis infantisepticum is frequently fatal regardless of treatment. Early-onset disease carries a higher mortality risk than late-onset infection, and immunocompromised hosts have a worse prognosis than do otherwise healthy adults with listeriosis.

## PREVENTION

*L. monocytogenes* is frequently isolated from food; the Food and Drug Administration, the U.S. Department of Agriculture, and manufacturers are pursuing further measures to reduce *L. monocytogenes* contamination of foods that have been subjected to listericidal processing. Prevention of listeriosis requires dietary counseling of persons at increased risk of disease (Table 142-1). There is no role for the administration of prophylaxis to contacts of patients with listeriosis. Clinicians are encouraged to report cases of listeriosis to local or state health departments. Case reporting and subtyping of clinical isolates can facilitate early recognition of outbreaks and prevention of subsequent cases.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 143. TETANUS - *Elias Abrutyn*

### DEFINITION

Tetanus is a neurologic disorder, characterized by increased muscle tone and spasms, that is caused by tetanospasmin, a powerful protein toxin elaborated by *Clostridium tetani*. Tetanus occurs in several clinical forms, including generalized, neonatal, and localized disease.

### ETIOLOGIC AGENT

*C. tetani* is an anaerobic, motile gram-positive rod that forms an oval, colorless, terminal spore and thus assumes a shape resembling a tennis racket or drumstick. The organism is found worldwide in soil, in the inanimate environment, in animal feces, and occasionally in human feces. Spores may survive for years in some environments and are resistant to various disinfectants and to boiling for 20 min. Vegetative cells, however, are easily inactivated and are susceptible to several antibiotics (metronidazole, penicillin, and others).

Tetanospasmin is formed in vegetative cells under plasmid control. It is a single-polypeptide chain. With autolysis, the single-chain toxin is released and cleaved to form a heterodimer consisting of a heavy chain (100 kDa), which mediates binding to nerve-cell receptors and entry into these cells, and a light chain (50 kDa), which acts to block neurotransmitter release. The amino acid structures of the two most powerful toxins known, botulinum toxin and tetanus toxin, are partially homologous.

### EPIDEMIOLOGY

Tetanus occurs sporadically and almost always affects nonimmunized persons, partially immunized persons, or fully immunized individuals who fail to maintain adequate immunity with booster doses of vaccine. Although tetanus is entirely preventable by immunization, the burden of disease is large worldwide. The disease is common in areas where soil is cultivated, in rural areas, in warm climates, during summer months, and among males. In countries without a comprehensive immunization program, tetanus occurs predominantly in neonates and other young children; an estimated 490,000 neonates died of tetanus worldwide in 1994 -- a reduction from 550,000 in 1993. In the United States and other nations with successful immunization programs, neonatal tetanus is rare and the disease affects other age groups and groups inadequately covered by immunization (such as nonwhites). The risk for the development of tetanus and for the most severe illness is highest among the elderly. Only 27% of persons aged 70 or older -- as opposed to 88% of 6- to 11-year-olds -- have protective antibody levels. During the years 1995 through 1997, a total of 124 cases were reported to the Centers for Disease Control and Prevention; both the overall incidence (0.15 cases per 100,000 population) and the annual average (41 cases) were the lowest ever reported in the United States. The actual burden of illness, however, was greater, because reporting is incomplete. Although the elderly customarily account for the highest proportion of cases, in 1995 through 1997 individuals ³60 years of age accounted for only 35% of cases, whereas those 20 to 59 years of age accounted for 60% and those under 20 for 5% (with one case of neonatal tetanus). The change is attributed to a decrease in incidence

in both the ³60 and the<20 age groups, along with an increase among persons 20 to 59 years of age, particularly injection drug users.

In the United States, most cases of tetanus follow an acute injury, such as a puncture wound, laceration, or abrasion. Tetanus is acquired indoors or during farming, gardening, and other outdoor activities. The injury may be major but often is trivial, so that medical attention is not sought; in some instances no injury can be identified. The disease may complicate chronic conditions such as skin ulcers, abscesses, and gangrene. Tetanus is also associated with burns, frostbite, middle-ear infection, surgery, abortion, childbirth, and drug abuse, notably "skin popping." In some patients no portal of entry for the organism can be identified.

## PATHOGENESIS

Contamination of wounds with spores of *C. tetani* is probably frequent. Germination and toxin production, however, take place only in wounds with low oxidation-reduction potential, such as those with devitalized tissue, foreign bodies, or active infection. *C. tetani* does not itself evoke inflammation, and the portal of entry retains a benign appearance unless infection with other organisms is present.

Toxin released in the wound binds to peripheral motor neuron terminals, enters the axon, and is transported to the nerve-cell body in the brainstem and spinal cord by retrograde intraneuronal transport. The toxin then migrates across the synapse to presynaptic terminals, where it blocks release of the inhibitory neurotransmitters glycine andg-aminobutyric acid (GABA). The blocking of neurotransmitter release by tetanospasmin, a zinc metalloprotease, involves the cleavage of protein(s) critical to proper function of the synaptic vesicle release apparatus. With diminished inhibition, the resting firing rate of thea motor neuron increases, producing rigidity. With lessened activity of reflexes that limit polysynaptic spread of impulses (a glycinergic activity), agonists and antagonists may be recruited rather than inhibited, with the consequent production of spasms. Loss of inhibition may also affect preganglionic sympathetic neurons in the lateral gray matter of the spinal cord and produce sympathetic hyperactivity and high circulating catecholamine levels. Tetanospasmin, like botulinum toxin, may block neurotransmitter release at the neuromuscular junction and produce weakness or paralysis; recovery requires sprouting of new nerve terminals.

In local tetanus, only the nerves supplying the affected muscles are involved. Generalized tetanus occurs when toxin released in the wound enters the lymphatics and bloodstream and is spread widely to distant nerve terminals; the blood-brain barrier blocks direct entry into the central nervous system. If it is assumed that intraneuronal transport times are equal for all nerves, short nerves are affected before long nerves: this fact explains the sequential involvement of nerves of the head, trunk, and extremities in generalized tetanus.

## CLINICAL MANIFESTATIONS

*Generalized tetanus*, the most common form of the disease, is characterized by increased muscle tone and generalized spasms. The median time of onset after injury is 7 days; 15% of cases occur within 3 days and 10% after 14 days.

Typically, the patient first notices increased tone in the masseter muscles (trismus, or lockjaw). Dysphagia or stiffness or pain in the neck, shoulder, and back muscles appears concurrently or soon thereafter. The subsequent involvement of other muscles produces a rigid abdomen and stiff proximal limb muscles; the hands and feet are relatively spared. Sustained contraction of the facial muscles results in a grimace or sneer (risus sardonicus), and contraction of the back muscles produces an arched back (opisthotonos). Some patients develop paroxysmal, violent, painful, generalized muscle spasms that may cause cyanosis and threaten ventilation. These spasms occur repetitively and may be spontaneous or provoked by even the slightest stimulation. A constant threat during generalized spasms is reduced ventilation or apnea or laryngospasm. The severity of illness may be mild (muscle rigidity and few or no spasms), moderate (trismus, dysphagia, rigidity, and spasms), or severe (frequent explosive paroxysms). The patient may be febrile, although many have no fever; mentation is unimpaired. Deep tendon reflexes may be increased. Dysphagia or ileus may preclude oral feeding.

Autonomic dysfunction commonly complicates severe cases and is characterized by labile or sustained hypertension, tachycardia, dysrhythmia, hyperpyrexia, profuse sweating, peripheral vasoconstriction, and increased plasma and urinary catecholamine levels. Periods of bradycardia and hypotension may also be documented. Sudden cardiac arrest sometimes occurs, but its basis is unknown. Other complications include aspiration pneumonia, fractures, muscle rupture, deep vein thrombophlebitis, pulmonary emboli, decubitus ulcer, and rhabdomyolysis.

*Neonatal tetanus* usually occurs as the generalized form and is usually fatal if left untreated. It develops in children born to inadequately immunized mothers, frequently after unsterile treatment of the umbilical cord stump. Its onset generally comes during the first 2 weeks of life. Poor feeding, rigidity, and spasms are typical features of neonatal tetanus.

*Local tetanus* is an uncommon form in which manifestations are restricted to muscles near the wound. The prognosis is excellent.

*Cephalic tetanus*, a rare form of local tetanus, follows head injury or ear infection. Trismus and dysfunction of one or more cranial nerves, often the seventh nerve, are found. The incubation period is a few days and the mortality is high.

## DIAGNOSIS

The diagnosis of tetanus is based entirely on clinical findings. Tetanus is unlikely if a reliable history indicates the completion of a primary vaccination series and the receipt of appropriate booster doses. Wounds should be cultured in suspected cases. However, *C. tetani* can be isolated from wounds of patients without tetanus and frequently cannot be recovered from wounds of those with tetanus. The leukocyte count may be elevated. Cerebrospinal fluid examination yields normal results. Electromyograms may show continuous discharge of motor units and shortening or absence of the silent interval normally seen after an action potential. Nonspecific changes may be evident on the electrocardiogram. Muscle enzyme levels may be raised. Serum antitoxin levels of$^{3}$0.01

U/mL are considered protective and make tetanus unlikely, although cases developing despite protective antitoxin levels have been reported.

The differential diagnosis includes local conditions also producing trismus, such as alveolar abscess, strychnine poisoning, dystonic drug reactions (e.g., to phenothiazines and metoclopramide), and hypocalcemic tetany. Other conditions sometimes confused with tetanus include meningitis/encephalitis, rabies, and an acute intraabdominal process (because of the rigid abdomen). Markedly increased tone in central muscles (face, neck, chest, back, and abdomen) with superimposed generalized spasms and relative sparing of the hands and feet strongly suggests tetanus.

## TREATMENT

**General Measures** The goals of therapy are to eliminate the source of toxin, neutralize unbound toxin, and prevent muscle spasms, monitoring the patient's condition and providing support -- especially respiratory support -- until recovery. Patients should be admitted to a quiet room in an intensive care unit, where observation and cardiopulmonary monitoring can be maintained continuously but stimulation can be minimized. Protection of the airway is vital. Wounds should be explored, carefully cleansed, and thoroughly debrided.

**Antibiotic Therapy** Although of unproven value, antibiotic therapy is administered to eradicate vegetative cells -- the source of toxin. The use of penicillin (10 to 12 million units intravenously, given daily for 10 days) has been recommended, but metronidazole (500 mg every 6 h or 1 g every 12 h) is preferred by some experts on the basis of this drug's excellent antimicrobial activity, a survival rate higher than that obtained with penicillin in one nonrandomized trial, and the absence of theGABAantagonistic activity seen with penicillin. Clindamycin and erythromycin are also alternatives for the treatment of penicillin-allergic patients. Additional specific antimicrobial therapy should be given for active infection with other organisms.

**Antitoxin** Given to neutralize circulating toxin and unbound toxin in the wound, antitoxin effectively lowers mortality; toxin already bound to neural tissue is unaffected. Human tetanus immune globulin (TIG) is the preparation of choice and should be given promptly. The dose is 3000 to 6000 units intramuscularly, usually in divided doses because the volume is large. The optimal dose is not known, however, and results from one study indicated that a 500-unit dose was as effective as higher doses. Pooled intravenous immunoglobulin may be an alternative to TIG, but the specific antitoxin concentration in this formulation is not standardized. It may be best to administer antitoxin before manipulating the wound; the value of injecting a dose proximal to the wound or infiltrating the wound is unclear. Additional doses are unnecessary because the half-life of antitoxin is long. Antibody does not penetrate the blood-brain barrier. Intrathecal administration should be considered experimental. Equine tetanus antitoxin (TAT) is not available in the United States but is used elsewhere. It is cheaper than human antitoxin, but its half-life is shorter and its administration commonly elicits hypersensitivity and serum sickness.

**Control of Muscle Spasms** Many agents, alone and in combination, have been used to treat the muscle spasms of tetanus, which are painful and can threaten ventilation by

causing laryngospasm or sustained contraction of ventilatory muscles. The ideal therapeutic regimen would abolish spasmodic activity without causing oversedation and hypoventilation. Diazepam, a benzodiazepine andGABAagonist, is in wide use. The dose is titrated, and large doses (³250 mg/d) may be required. Lorazepam, with a longer duration of action, and midazolam, with a short half-life, are other options. Barbiturates and chlorpromazine are considered second-line agents. Therapeutic paralysis with a nondepolarizing neuromuscular blocking agent and mechanical ventilation may be required for the treatment of spasms unresponsive to medication or spasms that threaten ventilation. However, prolonged paralysis after the discontinuation of therapy with such agents has been described, and both the need for continued paralysis and the occurrence of complications should be assessed daily. Alternative agents include propofol, which is expensive, and dantrolene and baclofen, which are being investigated in the hope of shortening the period of therapeutic paralysis.

**Respiratory Care** Intubation or tracheostomy, with or without mechanical ventilation, may be required for hypoventilation due to oversedation or laryngospasm or for the avoidance of aspiration by patients with trismus, disordered swallowing, or dysphagia. The need for these procedures should be anticipated, and they should be undertaken electively and early.

**Autonomic Dysfunction** The optimal therapy for sympathetic overactivity has not been defined. Agents that have been considered include labetalol (ana- and b-adrenergic blocking agent that is recommended by some experts but that reportedly has caused sudden death), esmolol administered by continuous infusion (a beta blocker whose short half-life may be advantageous in the event of severe hypertension from unopposeda-adrenergic activity), clonidine (a central-acting antiadrenergic drug), and morphine sulfate. Parenteral magnesium sulfate and continuous spinal or epidural anesthesia have been used but may be more difficult to administer and monitor. The relative efficacy of these modalities has yet to be determined. Hypotension or bradycardia may require volume expansion, use of vasopressors or chronotropic agents, or pacemaker insertion.

**Vaccine** Patients recovering from tetanus should be actively immunized (see below) because immunity is not induced by the small amount of toxin that produces disease.

**Additional Measures** Additional therapeutic measures include hydration to control insensible and other fluid losses, which may be significant; the meeting of the patient's increased nutritional requirements by enteral or parenteral means; physiotherapy to prevent contractures; and administration of heparin or another anticoagulant to prevent pulmonary emboli. Bowel, bladder, and renal function must be monitored. Gastrointestinal bleeding and decubitus ulcers must be prevented, and intercurrent infection should be treated.

## PREVENTION

**Active Immunization** All partially immunized and unimmunized adults should receive vaccine, as should those recovering from tetanus. The primary series for adults consists of three doses: the first and second doses are given 4 to 8 weeks apart, and the third dose is given 6 to 12 months after the second. A booster dose is required every 10

years and may be given at mid-decade ages -- 35, 45, and so on. Combined tetanus and diphtheria toxoid (Td) adsorbed (for adult use), rather than single-antigen tetanus toxoid, is preferred for persons >7 years of age.

**Wound Management** Proper wound management requires consideration of the need for (1) passive immunization withTIG and (2) active immunization with vaccine, preferably Td in persons over age 7. For clean minor wounds, Td is administered to persons who (1) have unknown tetanus immunization histories; (2) have received fewer than three doses of adsorbed tetanus toxoid; (3) have received three or more doses of adsorbed vaccine, with the last dose given >10 years previously; and (4) have received three doses of *fluid* (nonadsorbed) vaccine. The recommendations for contaminated or severe wounds are identical, except that vaccine should be given to those who have received three or more doses of adsorbed tetanus toxoid if >5 years have elapsed since the last dose. Passive immunization with TIG is not recommended for clean minor wounds but is given for all other wounds if the patient's vaccination history indicates unknown or partial immunization. The dose of TIG for passive immunization of persons with wounds of average severity is 250 units intramuscularly, which produces a protective antibody level in the serum for at least 4 to 6 weeks; the appropriate dose ofTAT is 3000 to 6000 units. Vaccine and tetanus antitoxin should be administered at separate sites in separate syringes.

**Neonatal Tetanus** Measures aimed at preventing neonatal tetanus include maternal vaccination, even during pregnancy; efforts to increase the proportion of births that take place in the hospital; and the provision of training for nonmedical birth attendants.

## PROGNOSIS

The application of methods to monitor and support oxygenation has markedly improved the prognosis in tetanus; mortality rates as low as 10% have been reported from units accustomed to handling such cases. In the United States during the period 1995 through 1997, the case-fatality rate was 11%; 11 deaths from tetanus were reported in 1990, 11 in 1991, and 9 in 1992. The outcome is poor in neonates and the elderly and in patients with a short incubation period, a short interval from the onset of symptoms to admission, or a short period from onset of symptoms to the first spasm (period of onset). Outcome is also related to the extent of prior vaccination.

The course of tetanus extends over 4 to 6 weeks, and patients may require ventilatory support for 3 weeks during this period. Increased tone and minor spasms can last for months, but recovery is usually complete.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 144. BOTULISM - *Elias Abrutyn*

### DEFINITION

Botulism is a paralytic disease that begins with cranial nerve involvement and progresses caudally to involve the extremities. It is caused by potent protein neurotoxins elaborated by *Clostridium botulinum*. The toxins' high potency has led to consideration of their use in bioterrorism or biological warfare. Cases may be classified as (1) *food-borne botulism*, from ingestion of preformed toxin in food contaminated with *C. botulinum*; (2) *wound botulism*, from toxin produced in wounds contaminated with the organism; (3) *infant botulism*, from ingestion of spores and production of toxin in the intestine of infants; or (4) *adult infectious botulism*, a group that includes some cases in older children and adults in which disease is produced by a mechanism similar to that described for infant botulism.

### ETIOLOGIC AGENT

*C. botulinum*, a species encompassing a heterogeneous group of anaerobic gram-positive organisms that form subterminal spores, is found in soil and marine environments throughout the world and elaborates the most potent bacterial toxin known. Organisms of types A through G have been distinguished by the antigenic specificities of their toxins; a classification system based on physiologic characteristics has also been described. Rare strains of other clostridial species -- *C. butyricum* and *C. baratii* -- have also been found to produce toxin. *C. botulinum* strains with proteolytic activity can digest food and produce a spoiled appearance; nonproteolytic types leave the appearance of food unchanged.

Of the eight distinct toxin types described (A, B, $C_1$, $C_2$, D, E, F, and G), all except $C_2$ are neurotoxins; $C_2$ is a cytotoxin of unknown clinical significance. Botulinum neurotoxin, whether ingested or produced in the intestine or a wound, enters the vascular system and is transported to peripheral cholinergic nerve terminals, including neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. The central nervous system is not involved. Active neurotoxin (150 kDa) is composed of a heavy chain (a 100-kDa fragment responsible for neurospecific binding and translocation into the nerve cell) and a light chain (a 50-kDa fragment responsible for intracellular catalytic activity). The steps involved in neurotoxin activity include (1) specific binding to presynaptic nerve cells at the myoneural junction, (2) internalization of the toxin inside the nerve cell in endocytic vesicles, (3) translocation of the toxin into the cytosol, and (4) proteolysis by toxin (a zinc endopeptidase) of components of the neuroexocytosis apparatus curtailing release of the neurotransmitter acetylcholine. Cure follows sprouting of new nerve terminals.

Toxin is heat-labile, but spores are highly heat-resistant; both can be inactivated under appropriate conditions (see "Prevention," below). In the gastrointestinal tract, toxin is complexed with nontoxin proteins and resists degradation.

Toxin types A, B, E, and (in rare instances) F cause human disease; type G (now called *C. argentinense*) has been associated with sudden death, but not with neuroparalytic illness, in a few patients in Switzerland; and types C and D cause animal disease.

## EPIDEMIOLOGY

Human botulism occurs worldwide. In the United States, the geographic distribution of cases by toxin type parallels the distribution of organism types found in the environment. Type A predominates west of the Rocky Mountains; type B is generally distributed but is more common in the East; and type E is found in the Pacific Northwest, Alaska, and the Great Lakes area. In the United States, food-borne botulism has been associated primarily with home-canned food, particularly vegetables, fruit, and condiments, and less commonly with meat and fish. Type E outbreaks are frequently associated with fish products. Commercial products occasionally cause outbreaks, but some of these outbreaks have resulted from improper handling after purchase. Outbreaks in restaurants, schools, and private homes have been traced to uncommon sources (commercial potpies, beef stew, turkey loaf, sauteed onions, baked potatoes, and chopped garlic in oil). Food-borne botulism can occur when (1) a food to be preserved is contaminated with spores, (2) preservation does not inactivate the spores but kills other putrefactive bacteria that might inhibit the growth of *C. botulinum* and provides anaerobic conditions at a pH and temperature that allow germination and toxin production, and (3) food is not heated to a temperature that destroys toxin before being eaten.

## CLINICAL MANIFESTATIONS

**Food-Borne Botulism** Following ingestion of food containing toxin, illness varies from a mild condition for which no medical advice is sought to very severe disease that can result in death within 24 h. The incubation period is usually 18 to 36 h but, depending on toxin dose, can extend from a few hours to several days. Symmetric descending paralysis is characteristic and can lead to respiratory failure and death. Cranial nerve involvement, which almost always marks the onset of symptoms, usually produces diplopia, dysarthria, and/or dysphagia. Weakness progresses, often rapidly, from the head to involve the neck, arms, thorax, and legs; the weakness is occasionally asymmetric. Nausea, vomiting, and abdominal pain may precede or follow the onset of paralysis. Dizziness, blurred vision, dry mouth, and very dry, occasionally sore throat are common. Patients are generally alert and oriented, but they may be drowsy, agitated, and anxious. Typically, they have no fever. Ptosis is frequent; the pupillary reflexes may be depressed, and fixed or dilated pupils are noted in half of patients. The gag reflex may be suppressed, and deep tendon reflexes may be normal or decreased. Paralytic ileus, severe constipation, and urinary retention are common.

**Wound Botulism** When wounds are contaminated with *C. botulinum* spores, the spores may germinate into vegetative organisms that produce toxin. This rare condition resembles food-borne illness except that the incubation period is longer, averaging about 10 days, and gastrointestinal symptoms are lacking. Wound botulism has been documented after traumatic injury involving contamination with soil; in injection drug users, for whom black-tar heroin use has been identified as a risk factor; and after cesarean delivery. The illness has occurred even after antibiotics have been given to prevent wound infection. When present, fever is probably attributable to concurrent infection with other bacteria. The wound may appear benign.

**Infant Botulism** In infant botulism, the most common form of the disease, toxin is produced in and absorbed from the intestine after the germination of ingested spores. The severity ranges from mild illness with failure to thrive to fulminant severe paralysis with respiratory failure and may be one cause of sudden infant death. The identification of contaminated honey as one source of spores has led to the recommendation that honey not be fed to children<12 months of age. Most cases cannot be attributed to a particular food source. The factors permitting intestinal colonization with *C. botulinum* are not fully defined, but cases usually involve infants<6 months of age; susceptibility may decrease as the normal intestinal flora develops.

**Adult Infectious Botulism** Rarely, botulism in adults is produced by a mechanism similar to that operative in infant botulism: intestinal colonization and toxin production. The patient may have a history of gastrointestinal disease, surgery, or recent antibiotic therapy. Toxin and organisms may be identified in the stool.

## DIAGNOSIS

A diagnosis of botulism must be considered in afebrile, mentally intact patients who have symmetric descending paralysis without sensory findings. The diagnosis must be suspected on clinical grounds in the context of an appropriate history. Conditions often confused with botulism include myasthenia gravis, which may be ruled out by electromyography and antibody studies, and Guillain-Barre syndrome, which is characterized by ascending paralysis, sensory abnormalities, and elevation of the protein concentration in cerebrospinal fluid. The Fisher variant of Guillain-Barre -- a descending paralysis -- can indeed be difficult to differentiate from botulism. Other conditions that may resemble botulism include Lambert-Eaton syndrome, poliomyelitis, tick paralysis, diphtheria, and intoxications from mushrooms, medications, or chemicals. Hypermagnesemia should be considered.

The demonstration of toxin in serum by bioassay in mice is definitive, but this test may be negative, particularly in wound and infant botulism. It is performed only by specific laboratories, which can be identified through regional public health authorities. Other assays are being developed and remain experimental. The demonstration of the organism or its toxin in vomitus, gastric fluid, or stool is strongly suggestive of the diagnosis, because intestinal carriage is rare. Isolation of the organism from food without toxin is insufficient grounds for the diagnosis. Wound cultures yielding the organism are suggestive of botulism. The edrophonium chloride (Tensilon) test for myasthenia gravis may be falsely positive in botulism but is usually less dramatically positive than in the former condition. Nerve conduction velocity is normal, but compound muscle action potentials on routine nerve stimulation studies are decreased with a supramaximal stimulus, and facilitation is evident after repetitive stimulation at high frequency. Single-fiber electromyography may be helpful. The white blood cell count and erythrocyte sedimentation rate are normal.

## TREATMENT

Patients should be hospitalized and monitored closely, both clinically and by spirometry, pulse oximetry, and measurement of arterial blood gases for incipient respiratory failure. Intubation and mechanical ventilation should be strongly considered when the vital

capacity is <30% of predicted, especially when paralysis is progressing rapidly and hypoxemia with absolute or relative hypercarbia is documented (Chap. 266). Serial measurements of the maximal static inspiratory pressure may be useful in predicting respiratory failure.

In food-borne illness, trivalent (types A, B, and E) equine antitoxin should be administered as soon as possible after specimens are obtained for laboratory analysis. The initiation of treatment should not await laboratory confirmation, which may take days. After testing for hypersensitivity to horse serum, a vial of antitoxin is given; repeated doses are not considered necessary. Anaphylaxis and serum sickness are risks inherent in use of the equine product, and desensitization of allergic patients may be required. If there is no ileus, cathartics and enemas may be given to purge the gut of toxin; emetics or gastric lavage can also be used if the time since ingestion is brief (only a few hours). Use of antibiotics to eliminate an intestinal source for possible continued toxin production and of guanidine hydrochloride and other drugs to reverse paralysis is of unproven value. In the United States, antitoxin as well as help in clinical management and laboratory confirmation are available at *any* time from state health departments or from the Centers for Disease Control and Prevention [at (404)639-2206; emergency number: (404)639-2888].

Treatment of infant botulism requires supportive care. Neither equine antitoxin nor antibiotics have been shown to be beneficial, and the value of human botulism immune globulin, an experimental preparation, is still being evaluated. In wound botulism, equine antitoxin is administered. The wound should be thoroughly explored and debrided, and an antibiotic such as penicillin should be given to eradicate *C. botulinum* from the site, even though the benefit of this therapy is unproven. Results of wound cultures should guide the use of other antibiotics.

Botulinum toxin is being used as therapy for strabismus, blepharospasm, and other dystonias and appears safe and effective. Generalized botulism-like weakness complicating therapy has been reported.

## PROGNOSIS

Type A disease is generally more severe than type B, and mortality from botulism is higher among patients above age 60 than among younger patients. With improved respiratory and intensive care, the case-fatality rate in food-borne illness has been reduced to ~7.5% and is low in infant botulism as well. Artificial respiratory support may be required for months in severe cases. Some patients experience residual weakness and autonomic dysfunction for as long as a year after disease onset.

## PREVENTION

A pentavalent vaccine (A-E) is available for use in highly exposed individuals. Spores can be inactivated by exposure to a temperature of 116° to 121°C (e.g., in steam sterilizers or pressure cookers). Toxin can be inactivated by exposure to a temperature of 100°C for 10 min. Newly identified cases should be reported immediately to public health authorities.

(Bibliography omitted in Palm version)

Back to Table of Contents

# 145. GAS GANGRENE, ANTIBIOTIC-ASSOCIATED COLITIS, AND OTHER CLOSTRIDIAL INFECTIONS - *Dennis L. Kasper*, *Dori F. Zaleznik*

## DEFINITION

Bacteria of the genus *Clostridium* are gram-positive, spore-forming, obligate anaerobes that are ubiquitous in nature. There are more than 60 recognized species of clostridia, many of which are generally considered saprophytic. Some of these species are pathogenic for humans and animals, particularly under conditions of lowered oxidation-reduction potential. Infections associated with these organisms range from localized wound contamination to overwhelming systemic disease. The four major disease categories for which clostridia are responsible are intestinal disorders, deep tissue suppurative infections, skin and soft tissue infections, and bacteremia (Table 145-1). Toxins play a major role in some of these syndromes.

## ETIOLOGY

In humans, clostridia normally reside in the gastrointestinal tract and in the female genital tract, although they occasionally are isolated from the skin or the mouth. Of the known species of the genus *Clostridium*, at least 30 have been isolated from human infections. Like several other pathogenic anaerobic bacterial species, clostridia are quite aerotolerant, but they do not grow on artificial media in the presence of oxygen. Clostridia characteristically produce abundant gas in artificial media and form subterminal endospores. *C. perfringens*, one of the most important species, is encapsulated and nonmotile and rarely sporulates in artificial media; the spores can usually be destroyed by boiling. *C. tetani* and *C. botulinum* are discussed in detail in Chaps. 143 and144, respectively.

Clostridia are present in the normal colonic flora at concentrations of $10^9$ to $10^{10}$ per gram. Of the 30 or more species that normally colonize humans, *C. ramosum* is the most common and is followed in frequency by *C. perfringens*. These organisms are universally present in soil at concentrations of up to $10^4$ per gram. Although clostridia are gram-positive organisms, many species may appear to be gram-negative in clinical specimens or stationary-phase cultures. Therefore, the results of Gram's staining of cultures or clinical material should be interpreted with great care.

*C. perfringens* is the most common of the clostridial species isolated from tissue infections and bacteremias; next in frequency are *C. novyi* and *C. septicum*. In the category of enteric infections, *C. difficile* is an important cause of antibiotic-associated colitis, and *C. perfringens* is associated with food poisoning (type A) and enteritis necroticans (type C).

## PATHOGENESIS

Despite the isolation of clostridial species from many serious traumatic wounds, the prevalence of severe infections due to these organisms is low. Two factors that appear to be essential to the development of severe disease are tissue necrosis and a low oxidation-reduction potential. *C. perfringens* requires about 14 amino acids and at least 6 additional growth factors for optimal growth. These nutrients are not found in

appreciable concentrations in normal body fluids but are present in necrotic tissue. When *C. perfringens* grows in necrotic tissue, a zone of tissue damage due to the toxins elaborated by the organism allows progressive growth. In contrast, when only a few bacteria leak into the bloodstream from a small defect in the intestinal wall, the organisms do not have the opportunity to multiply rapidly because blood as a medium for growth is relatively deficient in certain amino acids and growth factors. Therefore, in a patient without tissue necrosis, bacteremia is usually benign.

*C. perfringens* possesses at least 17 possible virulence factors, including 12 active tissue toxins and enterotoxins. This species has been divided into five types (A through E) on the basis of four major lethal toxins: a,b, e, andi. The a toxin is a phospholipase C (lecithinase) that splits lecithin into phosphorylcholine and diglyceride. This a toxin has been associated with gas gangrene and is known to be hemolytic, to destroy platelets and polymorphonuclear leukocytes (PMNs), and to cause widespread capillary damage. When injected intravenously, it causes massive intravascular hemolysis and damages liver mitochondria. The a toxin may be important in the initiation of muscle infections that may progress to gas gangrene. Experimentally, the higher the concentration ofa toxin in the culture fluid, the smaller the dose of *C. perfringens* required to produce infection. The protective effect of antiserum is directly proportional to its content of aantitoxin. Studies suggest that q toxin may also play an important role in pathogenesis by promoting vascular leukostasis, endothelial cell injury, and regional tissue hypoxia. The resulting perfusion defects extend the anaerobic environment and contribute to rapidly advancing tissue destruction. A characteristic pathologic finding in gas gangrene is the near absence of PMNs despite extensive tissue destruction. Experimental data indicate that both a and q toxins are essential in the leukocyte aggregation that occurs at the margins of tissue injury instead of the expected infiltration of these cells into the area of damage. Genetically altered strains induce less leukocyte aggregation whena toxin is absent and none whenq toxin is missing. The other major toxins,b, e, andi, are known to increase capillary permeability.

*C. difficile* produces two major toxins, designated A and B. Both toxins appear to act by the same mechanism, but toxin B is 1000 times more potent. These toxins exert their effect by binding to small guanosine triphosphate-binding proteins in the Rho family within target cells. The toxins are uridine diphosphoglucose hydrolases and glucosyltransferases that glycosylate the guanosine triphosphatases, inactivating these proteins and resulting in disruption of actin. Once the actin filaments are destroyed, the cell is unable to function. Toxin B has 100-fold greater enzymatic activity than toxin A.

Diarrheal disease due to *C. difficile* is toxin-mediated. Earlier teaching about the pathogenesis of this disease centered on the overgrowth of *C. difficile* when antibiotics suppress the normal bowel flora. Actually, the mechanism is probably more complex, since many of the antibiotics that cause this disease are active against *C. difficile* as well as other members of the bowel flora and since many patients who become colonized with *C. difficile* do not develop diarrhea. Critical features in the pathogenesis of this disease include mechanisms of toxin production and the interaction of *C. difficile* with other components of the bowel flora. Some antibiotics may actually trigger toxin production by the organism. In turn, other constituents of the bowel flora may suppress or inhibit toxin production. *C. sordellii*, for example, neutralizes cytotoxin B in vitro. In addition, when antibiotics eliminate more sensitive members of the bowel flora, more

resistant organisms may produce enzymes such as b-lactamases that can inactivate antibiotics and thereby facilitate the growth of *C. difficile*.

## CLINICAL MANIFESTATIONS

### Intestinal Disorders

*Food Poisoning C. perfringens*, primarily type A, is the second or third most common cause of food poisoning in the United States (Chap. 131). The responsible toxin is thought to be a cytotoxin produced by more than 75% of strains isolated from cases of foodborne disease. The cytotoxin binds to a receptor on the small-bowel brush border and induces a calcium ion-dependent alteration in permeability. The associated loss of ions alters intracellular metabolism, resulting in cell death. Outbreaks generally have resulted from problems in the cooling and storage of food cooked in bulk. The food sources primarily involved are meat, meat products, and poultry. Generally, the implicated meats have been cooked, allowed to cool, and then recooked the following day, often in a stew or hash. Strains of *C. perfringens* that contaminate meat manage to survive initial cooking. During reheating, the organisms sporulate and germinate. The disease is associated with an attack rate that is often as high as 70%. Symptoms of food poisoning from type A strains develop 8 to 24 h after ingestion of foods heavily contaminated with the organism. The primary symptoms include epigastric pain, nausea, and watery diarrhea usually lasting 12 to 24 h. Fever and vomiting are uncommon. Molecular methods including ribotyping and pulsed-field gel electrophoresis have been used to detect fecal cytotoxin in outbreaks of food poisoning caused by *C. perfringens*.

*C. perfringens* has also been implicated in a more severe form of diarrhea than that of classic food poisoning. This more severe disease tends to occur in the elderly and has been associated with antibiotic use in hospitalized populations. In this form of disease, diarrhea is generally more profuse, of longer duration, and accompanied by abdominal pain. Blood and mucus have been detected in the feces of the affected patients. In one hospital-based study of a cluster of cases, widespread environmental contamination with *C. perfringens* spores was documented.

*Enteritis necroticans* Necrotizing enteritis (enteritis necroticans, or *pigbel*) is caused byb toxin produced by type C strains of *C. perfringens* following ingestion of a high-protein meal in conjunction with trypsin inhibitors (e.g., in sweet potatoes) by a susceptible host who has limited intestinal proteolytic activity. This disease has been reported among children and adults in New Guinea. A similar disease, *darmbrand*, was epidemic in Germany after World War II. Clinical features of pigbel include acute abdominal pain, bloody diarrhea, vomiting, shock, and peritonitis; 40% of patients die. Pathologic studies reveal an acute ulcerative process of the bowel restricted to the small intestine. The mucosa is lifted off the submucosa, with the formation of large denuded areas. Pseudomembranes composed of sloughed epithelium are common, and gas may dissect into the submucosa. The source of the organisms may be the patient's own intestinal flora; cultures of ingested pork have failed to yield the organism. Antibodies to the btoxin of *C. perfringens* have been of considerable benefit in changing the course of established disease. In a large-scale trial, children immunized with *C. perfringens* b toxoid were protected.

*Neutropenic enterocolitis (typhlitis)* See Chaps. 85 and167.

*Antibiotic-associated colitis* Strains of *C. difficile* that produce toxins detectable in the stool are the only identified cause of colitis induced by antibiotic use. The diagnosis of this type of colitis requires that there be no other identifiable cause of diarrhea and that the onset of symptoms occur either during antimicrobial administration or within 4 weeks after treatment with the implicated agent has been discontinued. Essentially any antibiotic can cause this syndrome; even metronidazole and vancomycin, which are used to treat the disease, have been implicated as etiologic agents in some cases. On a per-use basis, clindamycin, which was the first antibiotic described to cause this entity, is the most commonly implicated antibiotic. However, since other antibiotics are prescribed more often than clindamycin in the United States, cephalosporins are currently the antibiotics that most commonly cause *C. difficile* enterocolitis, and penicillins rank next in frequency. Diarrhea due to *C. difficile* has been reported in patients with some forms of malignancy or renal transplantation who have received tacrolimus without concomitant or previous antibiotic administration.

Antimicrobial-associated diarrhea can be divided into four categories based on the appearance of the colon: (1) normal colonic mucosa; (2) mild erythema with some edema; (3) granular, friable, or hemorrhagic mucosa; and (4) pseudomembrane formation. Most patients with antibiotic-associated diarrhea have a normal, minimally erythematous colonic mucosa with some edema. Occasionally, colitis is more severe and is characterized by a granular, friable, or hemorrhagic mucosa. Examination of stool from the affected patients may reveal large numbers of red blood cells and some leukocytes. Biopsy shows subepithelial edema with round cell infiltration of the lamina propria and focal extravasation of erythrocytes. *C. difficile* cytotoxin B has been found in 15 to 75% of stools from patients in the first three categories, which suggests that other factors are involved in the pathogenesis of antibiotic-associated diarrhea.

The most characteristic form of antibiotic-associated colitis caused by *C. difficile* is pseudomembranous colitis (PMC) (Fig. 145-CD1). More than 95% of patients with documented PMC have positive stool toxin assays. Close inspection of pseudomembranes reveals exudative, punctate, raised plaques with skip areas or edematous hyperemic mucosa. These plaques can enlarge and coalesce over large segments of intestine in the later stages of disease. The clinical spectrum of antibiotic-associated PMC is diverse. Diarrhea is the key feature; stools are usually watery, voluminous, and without gross blood or mucus. Most patients have abdominal cramps and tenderness, fever, and leukocytosis. However, the symptoms vary considerably. At one end of the spectrum are many patients with annoying diarrhea but no systemic signs or symptoms, while at the other end are those with severe systemic toxicity, fever (40° to 40.6°C, or 104° to 105°F), and peripheral white blood cell counts of up to 50,000/uL with a marked left shift. Fecal examination frequently reveals leukocytes. Without specific therapy, the course is highly variable. Some patients, particularly those with clinically mild disease, experience prompt resolution of symptoms with discontinuation of drug treatment, while others have protracted diarrhea with large stool volumes for up to 8 weeks, with resultant hypoalbuminemia and electrolyte imbalance. Severely ill patients with toxic megacolon and colonic perforation have been reported. Among patients who are severely ill mortality rates may be as high as 30%,

while in most of those with minimal symptoms disease may resolve with the discontinuation of antibiotic treatment alone. In the majority of patients, symptoms begin 4 to 10 days after antibiotic therapy is initiated. However, ~25% of patients do not develop symptoms until use of the implicated antimicrobial has been discontinued, in some instances as long as 4 weeks afterward. Some cases have been reported within hours after initiation of antibiotic therapy or after a single dose of antibiotic administered for surgical prophylaxis.

**Suppurative Deep Tissue Infections** Clostridia are frequently recovered from various suppurative conditions in conjunction with other anaerobic and aerobic bacteria but can also be the only organisms isolated. These suppurative conditions, which exist with severe local inflammation but usually without the characteristic systemic signs induced by clostridial toxins, include intraabdominal sepsis, empyema, pelvic abscess, subcutaneous abscess, frostbite with gas gangrene, infection of a stump in an amputee, brain abscess, prostatic abscess, perianal abscess, conjunctivitis, infection of a renal cell carcinoma, and infection of an aortic graft.

Clostridia are isolated from approximately two-thirds of patients with intraabdominal infections resulting from intestinal perforation. *C. ramosum*, *C. perfringens*, and *C. bifermentans* are the most commonly isolated species. The presence of clostridial species does not affect the clinical presentation or outcome of these infections (Chap. 167).

An association has been made between malignancy and the isolation of *C. septicum* in the absence of grossly contaminated deep traumatic wounds. A major site for such a malignancy is the gastrointestinal tract, particularly the colon. An association with leukemia or with other solid tumors has also been noted, and one case of fatal myonecrosis has been reported in a patient with ovarian cancer. Some of these patients present with *C. septicum* bacteremia; these cases have a fulminant clinical course (discussed below). Others develop localized suppurative infection in the abdomen or the abdominal wall without bacteremia. Presumably, this infection arises from a silent perforation that leads to intraabdominal abscess formation.

Clostridia have been isolated from suppurative infections of the female genital tract, particularly tuboovarian and pelvic abscesses. The major species involved has been *C. perfringens*. Most of these are mild suppurative infections without evidence of uterine gangrene. *C. perfringens* has been isolated from as many as 20% of diseased gallbladders at surgery. One clinical syndrome, emphysematous cholecystitis, is caused by clostridial species at least 50% of the time. In this syndrome, gas forms in the biliary radicles and the wall of the gallbladder. It is seen most often in diabetic patients. Although the mortality rate in this entity is higher than in more common forms of cholecystitis, there is no evidence of myonecrosis.

Clostridia are among the many organisms found in empyema fluid or isolated by transtracheal aspiration from patients with lung abscesses. There is no unique clinical clue to the presence of clostridia (as opposed to other organisms) in these infections. *C. perfringens* has been reported as a cause of empyema arising from aspiration pneumonia, pulmonary emboli, and infarction. However, the majority of cases of clostridial empyema are secondary to trauma.

**Skin and Soft Tissue Infections** Various categories of traumatic wound infections due to clostridia have been described: simple contamination, anaerobic cellulitis, fasciitis with or without systemic manifestations, and anaerobic myonecrosis.

*Simple contamination* Clostridia are cultured most often from wounds in the absence of clinical signs of sepsis. As many as 30% of battle wounds are contaminated by clostridia without signs of suppuration, and 16% of penetrating abdominal wounds yield clostridia on culture despite treatment with cephalothin and kanamycin. In cases of trauma, clostridia are isolated with equal frequency from suppurative and well-healing wounds. Thus the diagnosis of clostridial infection should be based on clinical rather than bacteriologic criteria.

*Localized infection of the skin and soft tissue without systemic signs* This condition, originally referred to as *anaerobic cellulitis*, is a localized infection involving the skin and soft tissue and is due to clostridia alone or with other bacteria. There are no systemic signs of toxicity, although the infection may invade locally, producing necrosis. These infections tend to be relatively indolent, spreading slowly to contiguous areas. Localized infections are relatively free of pain and edema. Perhaps because of the lack of edema, gas that is limited to the wound and the immediately surrounding tissue may be more evident than in gas gangrene. In these localized infections, gas is never found intramuscularly. Cellulitis, perirectal abscesses, and diabetic foot ulcers are typical infections from which clostridial species can be isolated. If inadequately treated, these localized infections advance by extension through subcutaneous tissue and fascial planes into muscle and may produce severe systemic disease with signs of toxemia.

A localized form of suppurative myositis has been described in heroin addicts. These patients develop local pain and tenderness in discrete areas (particularly the thigh and forearm), with the subsequent appearance of fluctuance and crepitance that require surgical drainage. The unusual aspect of these infections is that they remain localized without systemic signs of toxicity. Moreover, the affected local areas are not necessarily sites of trauma or heroin injection. Pathologic examination reveals subcutaneous abscesses, purulent myositis, and fasciitis from which clostridia are recovered in pure culture; on occasion, mixed infections involving aerobes and anaerobes are found. Wound botulism has been reported in association with the injection of black tar heroin.

*Spreading cellulitis and fasciitis with systemic toxicity* This condition involves diffuse spreading cellulitis and fasciitis, without myonecrosis and with only mild inflammation in muscle. Patients present with the abrupt onset of a syndrome that progresses rapidly (within hours) through the fascial planes. In cases with suppuration and gas in soft tissues as well as overwhelming toxemia, the infection is rapidly fatal. On physical examination there is subcutaneous crepitation but little localized pain. Surgery is of no proven value because there are no discretely involved tissues amenable to resection, as may be the case in myonecrosis. However, in rapidly advancing fasciitis, incision of the affected area is still the cornerstone of therapy. The initial local lesion may be quite innocuous and arises from an area involved by tumor or other infection and not by injury. The systemic toxic effects include hemolysis and injury of capillary membranes. Usually, this infection is uniformly fatal within 48 h, despite intensive therapy involving antitoxin and exchange transfusion. This syndrome is seen most commonly in patients

with carcinoma, especially of the sigmoid or the cecum. Presumably, the tumor invades the fascia, and colonic contents leak into the abdominal wall. Patients present with extreme toxicity and occasionally with total-body crepitation. The syndrome differs from necrotizing fasciitis caused by other organisms in three respects: (1) rapid mortality, (2) rapid tissue invasion, and (3) the systemic effects of the toxin, typified by massive hemolysis.

*Clostridial myonecrosis (gas gangrene) (Fig. 145-CD2)* Clostridial myonecrosis occurs when bacteria invade healthy muscle from adjacent traumatized muscle or soft tissue. The infection originates in a wound contaminated with clostridia. Although >30% of deep wounds are infected with clostridia, the incidence of clostridial myonecrosis is quite low. These infections occur in both military and civilian settings. An essential factor in the genesis of gas gangrene appears to be trauma, particularly involving deep muscle laceration. The entity of clostridial myonecrosis is relatively uncommon after simple, through-and-through bullet wounds without shattering of bone and is relatively common following shrapnel fragmentation wounds, particularly when deep muscle is involved. In civilian cases, gas gangrene can follow trauma, surgery, or intramuscular injection. The trauma need not be severe; however, the wound must be deep, necrotic, and without communication to the surface.

The incubation period of gas gangrene is usually short: almost always <3 days and frequently <24 h. Some 80% of cases are caused by *C. perfringens*, while *C. novyi*, *C. septicum*, and *C. histolyticum* cause most of the other cases. Typically, gas gangrene begins with the sudden onset of pain in the region of the wound, which helps to differentiate it from spreading cellulitis. Once established, the pain increases steadily in severity but remains localized to the infected area and spreads only if the infection spreads. Soon after pain develops, local swelling and edema -- accompanied by a thin, often hemorrhagic exudate -- appear. Patients frequently develop marked tachycardia, but elevation in temperature may be only minimal. Gas is usually not obvious at this early stage and may be completely absent. Frothiness of the wound exudate may be noted. The skin is tense, white, often marbled with blue, and cooler than normal. The symptoms progress rapidly; swelling, edema, and toxemia increase, and a profuse serous discharge, which may have a peculiar sweetish smell, appears. Gram's staining of the wound exudate shows many gram-positive rods with relatively few inflammatory cells.

At surgery, muscle may appear pale because of the intensity of edema, but it does not contract when probed with a scalpel. When dissected, the muscle is beefy red and nonviable and can progress to become black, friable, and gangrenous. It is important to establish a diagnosis early, preferably by frozen-section biopsy of muscle.

Despite hypotension, renal failure, and (often) body crepitation, patients with myonecrosis frequently have a heightened awareness of their surroundings until just before death, when they lapse into toxic delirium and coma. In untreated cases, as the local wounds progress, the skin becomes bronzed; bullae appear, become filled with dark red fluid, and are accompanied by dark patches of cutaneous gangrene. Gas appears in later phases (Fig. 145-1) but may not be as obvious as in anaerobic cellulitis. Jaundice is rare in wound gas gangrene (in contrast to uterine infections) and, when it does appear, is almost invariably associated with hemoglobinuria, hemoglobinemia, and

septicemia. Cases of clostridial myonecrosis without a history of trauma have been reported. These patients have bullous lesions and crepitation of the skin; they present with a rapidly worsening course that includes myonecrosis, especially of the extremities.

**Bacteremia and Clostridial Sepsis** The relatively common entity of transient clostridial bacteremia can arise in any hospitalized patient but is most common with a predisposing focus in the gastrointestinal tract, biliary tract, or uterus. Fever frequently resolves within 24 to 48 h without therapy. Despite the finding of clostridial bacteremia following septic abortions and the frequent isolation of clostridia from the lochia, most of the patients involved do not have evidence of sepsis. In one series of 60 patients with clostridial bacteremia, half had an infected site that could be associated with the bacteremia, while the other half had a totally unrelated illness, such as tuberculous pneumonia, meningitis, or benign gastroenteritis. By the time blood culture reports are returned, patients frequently are completely well and sometimes have been discharged. Therefore, when a blood culture is positive for clostridia, the patient must be assessed clinically rather than simply treated on the basis of the culture result.

Clostridial sepsis is an uncommon but almost invariably fatal illness following clostridial infection -- primarily that of the uterus, colon, or biliary tract. This entity must be differentiated from transient clostridial bacteremia, which is much more common. *C. perfringens* causes the majority of cases of sepsis as well as the majority of cases of transient bacteremia. *C. septicum*, *C. sordellii*, and *C. novyi* account for most of the remainder of cases. Clostridia account for 1 to 2.5% of all positive blood cultures in major hospital centers.

The majority of cases of clostridial sepsis originate from the female genital tract and follow septic abortion. Introduction of a foreign body is a common antecedent event. In the uterus, residual necrotic fetal and placental tissues and traumatized endometrium may allow the growth of clostridia. Only a small fraction of cases of septic abortion (1%) are followed by serious sepsis. In these patients, sepsis, fever, and chills begin from 1 to 3 days after the attempted abortion. The initial signs are malaise, headache, severe myalgias, abdominal pain, nausea, vomiting, and occasionally diarrhea. Frequently, a bloody or brown vaginal discharge is noted. Patients may rapidly develop oliguria, hypotension, jaundice, and hemoglobinuria. The hemolysis, which is secondary to *C. perfringens* a toxin, causes a characteristic bronzing of the skin. As in myonecrosis, the mental status of severely ill patients is characterized by increased alertness and apprehension. Local examination of the pelvis reveals foul cervical discharge, occasionally with gas. Frequently, laceration marks around the cervix or perforation of the cervical segment is evident. If the infection involves the myometrium or has spread to the adnexa, extreme tenderness, guarding, and an adnexal mass may be found.

Laboratory studies in patients with sepsis reveal an elevated white blood cell count and may show pink, hemoglobin-tinged plasma. Anemia is proportional to the degree of hemolysis, and the hematocrit may be extremely low. Platelet counts may be reduced, and there is often evidence of disseminated intravascular coagulation. Oliguria or anuria, increasingly refractory hypotension, and hemorrhage and bruising may develop.

Clostridia may enter the bloodstream from the gastrointestinal or biliary tract. This occurrence is associated with ulcerative lesions or obstruction of the small or large

intestine, necrotic or infiltrating malignancy, bowel surgery, or various abdominal catastrophes. The patient may present with an acute febrile illness, with chills and fever but no other signs of localized infection. Intravascular hemolysis occurs in as many as half of such cases. Biliary or gastrointestinal symptoms, if present, may be the only clue to the etiology. Positive blood cultures provide the definitive clue to the diagnosis.

Patients with malignant disease can also develop rapidly fatal clostridial sepsis, particularly from a gastrointestinal focus. The most common species in this setting is *C. septicum*. Characteristic signs and symptoms include fever, tachycardia, hypotension, abdominal pain or tenderness, nausea, vomiting, and (preterminally) coma. The tachycardia may be out of proportion to the fever. Only ~20 to 30% of patients develop hemolysis. A striking feature of this syndrome is the rapidity of death, which frequently occurs in <12 h.

## DIAGNOSIS

The diagnosis of clostridial disease, in association with positive cultures, must be based primarily on clinical findings. Because of the presence of clostridia in many wounds, their mere isolation from any site, including the blood, does not necessarily indicate severe disease. Smears of wound exudates, uterine scrapings, or cervical discharge may show abundant large gram-positive rods as well as other organisms. Cultures should be placed in selective media and incubated anaerobically for identification of clostridia. The diagnosis of clostridial myonecrosis can be established by frozen-section biopsy of muscle.

The urine of patients with severe clostridial sepsis may contain protein and casts, and some patients may develop severe uremia. Profound alterations of circulating erythrocytes are seen in severely toxemic patients. Patients have hemolytic anemia, which develops extremely rapidly, along with hemoglobinemia, hemoglobinuria, and elevated levels of serum bilirubin. Spherocytosis, increased osmotic and mechanical red blood cell fragility, erythrophagocytosis, and methemoglobinemia have been described. Disseminated intravascular coagulation may develop in patients with severe infection. In patients with severe sepsis, Wright's or Gram's staining of a smear of peripheral blood or buffy coat may demonstrate clostridia.

X-ray examination sometimes provides an important clue to the diagnosis by revealing gas in muscles, subcutaneous tissue, or the uterus. However, the finding of gas is not pathognomonic for clostridial infection. Other anaerobic bacteria, frequently mixed with aerobic organisms, may produce gas.

The diagnosis of *C. difficile*-associated colitis is most often made by an enzyme-linked immunosorbent assay (ELISA) for toxin A. Compared with the "gold standard" tissue culture assay used primarily for the detection of toxin B, the ELISA exhibits comparable specificity and only slightly lower sensitivity (70 to 90%). The cytotoxicity assay requires a tissue culture facility, skilled laboratory technicians, and time (usually 48 h), since neutralization of the cytopathic effect with *C. sordellii* or *C. difficile* antitoxin is required before the test can be labeled positive. ELISA is more rapid and easier to perform. However, in difficult situations where the clinical diagnosis remains a possibility and ELISA results are negative, consideration should be given to requesting the cytotoxicity

assay since it may detect 5 to 10% more cases. Repeat stool testing with the same assay generally does not increase the diagnostic yield for this entity. Endoscopy, although useful in establishing the presence ofPMC, does not establish the etiology and should be reserved for cases with more serious disease manifestations, in which it can be used to exclude alternative diagnoses. Isolation of *C. difficile* from stool cultures is difficult. This approach should be reserved for epidemiologic studies of outbreaks since asymptomatic persons may harbor the pathogen, but production of toxin is the hallmark of disease.

**TREATMENT**

Traumatic wounds should be thoroughly cleansed and debrided. Traditionally, the antibiotic treatment of choice for severe clostridial infection has been penicillin G (20 million units a day in adults). Penicillin G treatment of gas gangrene has become more controversial because of increasing resistance to this drug and data obtained from animal models of infection. In a mouse model of gas gangrene, antibiotics inhibiting toxin synthesis appeared to be preferable to cell wall-active drugs; clindamycin treatment enhanced survival more than therapy with penicillin; and the combination of clindamycin and penicillin was superior to penicillin alone. For severe clostridial sepsis, clindamycin may be used at a dose of 600 mg every 6 h in combination with high-dose penicillin (3 to 4 million units every 4 h). Although no clinical trials validate this choice, it is gaining acceptance in the infectious disease community.

In cases of penicillin sensitivity or allergy, other antibiotics should be considered, but all should be tested for in vitro activity because of the occasional isolation of resistant strains. Clostridia are frequently, but not universally, susceptible in vitro to cefoxitin, carbenicillin, chloramphenicol, clindamycin, metronidazole, doxycycline, imipenem, minocycline, tetracycline, third-generation cephalosporins, and vancomycin. For severe clostridial infections, sensitivity testing should be done before an antimicrobial with unpredictable activity is used. Simple contamination of a wound with clostridia should not be treated with antibiotics. Localized skin and soft tissue infection can be managed by debridement rather than with systemic antibiotics. Drugs are required when the process extends into adjacent tissue or when fever and systemic signs of sepsis are present. Surgery is a mainstay of therapy for clostridial myonecrosis or gas gangrene. Amputation may be required for rapidly spreading infection involving a limb. Hysterectomy is required for uterine myonecrosis. Abdominal wall myonecrosis usually continues despite initial aggressive surgery and antibiotic therapy and requires repeated surgical debridement of all involved muscle.

Suppurative infections should be treated with antibiotics. Frequently, broad-spectrum antibiotics must be used because of the mixed flora involved in these infections. Aminoglycosides can be used for the aerobic gram-negative bacteria involved in mixed infections.

The use of a polyvalent gas gangrene antitoxin is still recommended by some authorities. At present, no such antitoxin is produced in the United States, and most centers have discontinued its use in the management of patients with suspected gas gangrene or clostridial postabortion sepsis because of questionable efficacy and the substantial risk of hypersensitivity to horse serum, from which the antitoxin is derived.

The use of hyperbaric oxygen in the treatment of gas gangrene is also controversial. Studies in humans are not well designed to answer questions on efficacy, but several knowledgeable authors believe that hyperbaric oxygen therapy has contributed to dramatic clinical improvement. Such therapy may, however, be associated with untoward effects due to oxygen toxicity and high atmospheric pressure. Some centers without hyperbaric chambers have reported acceptable mortality rates; thus expert surgical and medical management and control of complications are probably the most important factors in the treatment of gas gangrene. Fasciotomy should not be delayed for hyperbaric oxygen therapy.

The treatment of *C. difficile*-associated colitis requires discontinuation of therapy with the offending antimicrobial agent. In some patients, symptoms will resolve over a period of 2 weeks if the infection is left untreated. However, specific therapy shortens the duration of symptoms.

Diarrhea due to *C. difficile* should be treated with metronidazole (500 mg orally tid for 10 to 14 days). A randomized trial comparing metronidazole (250 mg qid) with oral vancomycin showed equal efficacy and relapse rates of ~9% for both regimens. Since both treatment regimens are effective, metronidazole is preferred because it is far less costly and has not been linked to the development of vancomycin-resistant enterococci. When a patient relapses, antibiotic resistance should not be inferred since it is rare; a repeat course of metronidazole is appropriate. When a patient with *C. difficile*-associated diarrhea requires continued antibiotic treatment for a serious infection such as infective endocarditis, it is often reasonable to continue therapy against *C. difficile* for the duration of the offending antibiotic treatment course and for a full 10 to 14 days following its completion. When vancomycin is used for the treatment of *C. difficile*-associated diarrhea, the starting dose should be 125 mg orally qid, although doses as high as 500 mg qid can be used if needed. When a patient requires parenteral therapy for antibiotic-associated diarrhea, intravenous metronidazole can be administered. Vancomycin is effective only if used orally; the drug is poorly absorbed after oral administration. If patients continue to have diarrhea and have signs of systemic toxicity (e.g., fever and/or leukocytosis) after 48 h of treatment with metronidazole, it is reasonable to switch to vancomycin. For especially severe disease, some experts advocate treatment with both oral vancomycin and metronidazole, although there are no trials to support this regimen.

A number of patients who respond to initial therapy present with a relapse of symptoms and a repeat positive toxin assay. Relapses following therapy are much more frequent than failures to respond to initial therapy. Most relapses occur 3 to 10 days after discontinuation of treatment. Most relapsing patients respond to a second course of antibiotics, but some go on to suffer multiple relapses. A number of options are available in this situation. Some authors report success with tapering regimens of vancomycin given daily or every other day for 1 to 2 months to avoid relapse. The resin cholestyramine binds the cytotoxin of *C. difficile* and has been used with some success to treat severe cases. Since cholestyramine also binds vancomycin, the two agents should not be used in combination. Repopulation of the normal colonic flora has also been tried in relapsing disease. Ingestion of capsules of the yeast *Saccharomyces boulardii* showed some promise in one trial; oral lactobacilli have also been used in

uncontrolled studies. The administration of intravenous immunoglobulin has been tried with success in a few children and adults with relapsing infection, although this approach is not yet considered to be recommended therapy.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 6 -DISEASES CAUSED BY GRAM-NEGATIVE BACTERIA

## 146. MENINGOCOCCAL INFECTIONS - *Robert S. Munford*

### DEFINITION

*Neisseria meningitidis* is the etiologic agent of two life-threatening diseases: meningococcal meningitis and fulminant meningococcemia. Meningococci also cause pneumonia, septic arthritis, pericarditis, urethritis, and conjunctivitis. Most cases are potentially preventable by vaccination.

### ETIOLOGIC AGENT

*N. meningitidis* bacteria are gram-negative aerobic diplococci. Unlike the other neisseriae, they have a polysaccharide capsule. They are transmitted among humans, their only known habitat, via respiratory secretions. Colonization of the nasopharynx or pharynx is much more common than invasive disease.

### EPIDEMIOLOGY

Meningococcal disease occurs worldwide as isolated (sporadic) cases, institution- or community-based outbreaks, and large epidemics.

Meningococci are classified into serogroups based on the antigenicity of their capsular polysaccharides. Antigenicity reflects structural differences in these polysaccharides. Five serogroups (A, B, C, Y, and W-135) are responsible for>90% of cases of meningococcal disease worldwide. Serogroup A strains, which caused most of the large epidemics of meningococcal disease during the first half of the twentieth century, are now associated with recurring epidemics in sub-Saharan Africa and other locales in the developing world. Serogroups B, C, and Y cause most cases of sporadic and epidemic meningococcal disease in industrialized countries. In the United States and Canada during the 1990s, serogroup B was the most common cause of sporadic disease, while serogroup C was a more frequent cause of outbreaks. Serogroup Y has recently been isolated from almost one-third of cases of meningococcal disease in the United States. In general, patients with serogroup Y disease are older and more likely to have a chronic underlying illness than are patients with disease caused by other serogroups. Serogroups Y and W-135 are isolated more often than the other serogroups from patients with pneumonia.

One limitation of the serogroup classification is that the genes for capsule biosynthesis can be transferred from one strain to another, with consequent changes in the capsule structure of the recipient strain and therefore in its serogroup. Other methods for tracking meningococcal strains have thus become increasingly useful. Meningococcal serotypes and subtypes are defined by antigenic differences in specific outer-membrane proteins (OMPs), whereas multilocus enzyme electrophoresis classifies bacteria into electrophoretic types (ETs). Other techniques for establishing strain identity or nonidentity are pulsed-field gel electrophoresis and amplification of bacterial genomic sequences by polymerase chain reaction. The virulent III-1 clonal complex of serogroup A was first recognized in Nepal in 1983 to 1984; it spread to Mecca, then to

sub-Saharan Africa, and subsequently to temperate Africa. Increased virulence and epidemic potential have also been ascribed to the serogroup B ET-5 complex, which was first identified in Norway in the 1970s and later caused outbreaks in Europe, Cuba, and South and North America (most recently, in the Pacific Northwest). Serogroup C ET-24 (the ET-37 complex) has caused sporadic cases and outbreaks in Canada and the United States and in some analyses has been associated with high mortality and morbidity.

Meningococcal colonization of the nasopharynx (asymptomatic carriage) can persist for months. In nonepidemic periods, ~10% of healthy individuals are colonized. Factors that predispose individuals to colonization with *N. meningitidis* include residence in the same household with a person who has meningococcal disease or is a carrier, household or institutional crowding, active or passive exposure to tobacco smoke, and a recent history of a viral upper respiratory infection. These factors have also been associated with an increased risk of meningococcal disease.

In countries with temperate climates, the attack rate for sporadic meningococcal disease is ~1 case per 100,000 persons per year. Peak disease incidence coincides with the winter peak of respiratory viral illnesses. Disease attack rates are highest among infants 3 to 9 months of age (10 to 15 cases per 100,000 infants per year). Children also have higher attack rates than adults, and there is a second peak of incidence among teenagers, in whom outbreaks have often been tied to residence in barracks, dormitories, or other crowded conditions. Although the age-specific incidence is much lower among adults (<1 case per 100,000 persons per year), approximately one-third of all cases of sporadic meningococcal disease occur in individuals ³18 years of age. During epidemics, disease incidence increases disproportionately among teenagers and young adults and during the summer and autumn.

Meningococcal disease occurs more commonly in the household contacts of primary cases. The secondary attack rate is 400 to 1000 per 100,000 household members. School-based clusters of cases have also been described; the attack rate among school contacts of cases has been estimated at 2 to 4 cases per 100,000 exposed individuals. In outbreaks on college campuses, attack rates have been highest among students living in dormitories. Most secondary cases occur within 2 weeks of the primary case, although some may develop as long as several months later. Secondary cases account for <2% of all cases reported each year in the United States.

In an outbreak, the case isolates of *N. meningitidis* are identical when they are assessed by molecular typing methods. Recent outbreaks of meningococcal disease have occurred among persons whose common exposure took place in military barracks, schools, a university campus tavern, a jail, a school bus, a disco bar, a sports club, and a hotel.

## PATHOGENESIS

Meningococci that colonize the upper respiratory tract are internalized by nonciliated mucosal cells and may traverse them to enter the submucosa, from which they can make their way into the bloodstream. While meningococcal colonization occurs often in healthy humans, bloodstream infection is an infrequent event that is not essential for the

organisms' survival and spread; as is often the case, the production of human disease has no obvious evolutionary advantage for either pathogen or host. Although some strains of *N. meningitidis* are thought to cause more severe disease in humans than do other strains, the basis for this difference is not understood. Meningococci may undergo important phenotypic changes when they adapt to growth in vivo; presumed virulence traits include the antiphagocytic capsular polysaccharide, an ability to sialylate the cell wall lipooligosaccharide (LOS) so that it mimics host cell carbohydrate moieties, the secretion of IgA protease, and mechanisms for iron acquisition. TheET-5 strain of serogroup B *N. meningitidis* has been associated with high case-fatality rates in some populations but not in others, however, suggesting that host factors also contribute importantly to disease pathogenesis.

A meningococcus that enters the blood from the nasopharynx and survives host defenses generally has one of two fates. If multiplication occurs slowly, the bacteria eventually seed local sites, such as the meninges, joints, or pericardium. More rapid multiplication in the blood is associated with disseminated intravascular coagulation (DIC) and shock, which usually cause symptoms before local sites become infected. There is thus a remarkable compartmentalization of bacterial growth and host inflammation in either the blood or a local site, usually the meninges.

**Fulminant Meningococcemia (Purpura Fulminans)** Fulminant meningococcemia is perhaps the most rapidly lethal form of septic shock experienced by humans. It differs from most other forms of septic shock by the prominence of hemorrhagic skin lesions (petechiae, purpura) and the consistent development ofDIC.

The dominant proinflammatory molecule in the meningococcal cell wall is the endotoxin orLOS, and the outer membrane that contains it is poorly tethered to the underlying peptidoglycan. This structural peculiarity seems to account for the fact that meningococci shed LOS-containing membrane blebs as they grow. The bacteria can multiply to very high concentrations in the blood. The concentrations of endotoxin detected in the blood of patients with fulminant meningococcemia are 10- to 1000-fold greater than those found in the blood of patients with bacteremia due to other gram-negative bacteria. The bacteria and endotoxin-containing blebs stimulate monocytes, neutrophils, and endothelial cells, which then release cytokines and other mediators that can activate many distant targets, including other leukocytes and endothelial cells. In addition, meningococci can invade the vascular endothelium. When activated, the endothelium produces molecules that can be procoagulant as well as adhesive for leukocytes.

Patients with fulminant meningococcemia usually have extremely high blood levels of both proinflammatory mediators -- i.e., tumor necrosis factor (TNF)a, interleukin (IL) 1, interferong, and IL-8 -- and anti-inflammatory mediators -- i.e., IL-1 receptor antagonist (IL-1Ra), soluble IL-1 receptors, soluble TNF receptors, and IL-10. The plasma of patients with meningococcal shock can decrease the responses of normal leukocytes to stimuli such asLOS; the implication is that anti-inflammatory mediators predominate in the blood.

Procoagulant, antifibrinolytic forces are predominant in the blood of patients with fulminant meningococcemia (Fig. 146-1). Monocytes express large amounts of tissue

factor. Fibrinopeptide A and thrombin-antithrombin levels are high, reflecting active clotting, while antithrombin and fibrinogen levels are low. Although the tissue factor-regulated ("extrinsic") arm of coagulation predominates, the contact system (factors XII and XI, prekallikrein, high-molecular-weight kininogen) is also activated. Striking deficiencies of antithrombin and proteins C and S can occur; studies have found a strong negative correlation between protein C activity and both the size of purpuric skin lesions and mortality. Plasminogen levels are decreased, while plasmin-antiplasmin complexes and plasminogen activator inhibitor 1 (PAI-1) levels in the blood are very high. PAI-1 levels have been correlated with mortality risk, as has a function-related polymorphism in the promoter of the PAI-1 gene.

Fibrin deposition is therefore favored both by the *procoagulant* tendency, promoted through activation of tissue factor and deficiencies of proteins C and S and antithrombin, and by an *antifibrinolytic* tendency, favored by excessivePAI-1. Both platelets and leukocytes doubtless contribute to the formation of microthrombi and to the vascular injury that ensues. Thrombosis of larger vessels leads to peripheral necrosis and gangrene that may require limb or digit amputation.

None of the candidate mediators of septic shock has proven primacy (Chaps. 38 and124). Numerous studies have suggested that shock andDIC are not intimately linked and that the contact arm of clotting, which is of secondary importance in the pathogenesis of DIC, plays at least a contributory role in the pathogenesis of shock. The independence of DIC and shock suggests that therapies that prevent or reverse DIC may not be helpful for patients with septic shock.

**Meningitis** *N. meningitidis* has a striking tropism for the meninges. Infection of the central nervous system begins in the choroid plexus or in the ependyma that lines the cerebral ventricles. Meningococci adhere to cerebral capillary endothelial cells and then enter the subarachnoid space. A vigorous local inflammatory response ensues, probably triggered by endotoxin-containing meningococcal membranes. Both bacterial growth and the inflammatory response occur within the cerebrospinal fluid (CSF), where levels of endotoxin,IL-6,TNF-a, IL-1b, IL-1Ra, and IL-10 exceed the concentrations found in plasma by 100- to 1000-fold. The inflammatory response is largely confined to the subarachnoid space and contiguous structures.

Patients who develop meningitis may be individuals in whom meningococci do not grow rapidly in the blood; they may have a more vigorous initial inflammatory response to invading meningococci, may have antibodies or phagocytes that slow meningococcal growth, or may lack the (unknown) factors that allow *N. meningitidis* to multiply rapidly in vivo. The prognosis of patients with meningococcal meningitis is substantially better than that of patients with fulminant meningococcemia (Table 146-1).

## HOST DEFENSE MECHANISMS

Preventing meningococcal growth in blood requires bactericidal and opsonic antibodies, complement, and phagocytes (Fig. 146-2). The major bactericidal antibodies are IgM and IgG, which bind to the capsular polysaccharide. Immunity to meningococci is therefore serogroup specific. Antibodies to other surface (subcapsular) antigens may confer cross-serogroup protection. Infants are protected from meningococcal disease

during the first months of life by passively transferred maternal IgG antibodies. As maternal antibody levels wane, the attack rate increases, peaking from 3 to 9 months of age. Disease incidence declines as protective antibodies are induced by colonization with nonpathogenic bacteria that have cross-reactive antigens. In addition to *N. lactamica*, which frequently colonizes young children, some enteric bacteria have antigens that cross-react with those of meningococci. One theory relates the occurrence of meningococcal disease to the presence of high levels of IgA antibodies to meningococci, since these antibodies can block the bactericidal activity of IgM.

Complement is required for bactericidal activity and for efficient opsonophagocytosis. Individuals deficient in any of the late complement components (C5 to C9) cannot assemble the membrane attack complex needed to kill *Neisseria*. These persons typically develop less severe meningococcal disease than complement-sufficient individuals, do so at an older age, and tend to have disease due to uncommon serogroups (W-135, X, Y, Z, and 29E). Although only one-half of individuals with known late-complement-component deficiency ever experience meningococcal disease, some affected persons have several episodes. Deficiency of each of the terminal complement components is inherited in an autosomal recessive fashion. Properdin deficiency, in contrast, is X-linked; some affected males develop overwhelming meningococcal disease, an observation indicating that the alternative complement pathway is also needed for antimeningococcal host defense. The age of disease onset in properdin-deficient individuals is typically in the teens or twenties.

Activation of the classic pathway of complement by antigen-antibody complexes or of the alternative pathway byLOS or capsular polysaccharide is important for producing and maintaining C3b (Fig. 146-2). Without C3b, neither bactericidal lysis nor phagocytosis can proceed effectively. When C3b is generated, meningococcal growth is probably checked by the membrane attack complex, which produces bacterial lysis, and by robust phagocytosis. Most IgG antibodies to the meningococcal polysaccharide are of the $IgG_2$isotype; a phagocytic cell defect (the FcgRIIA R131 allele) that impairs the phagocytosis of $IgG_2$-coated particles has been associated with more severe meningococcal disease. This allele has also been associated with a more severe clinical course in patients with late-complement-component deficiency; thus effective phagocytosis may contribute to the relatively mild meningococcal disease usually observed in these individuals.

Indirect evidence indicates that persons who mount a vigorous inflammatory response to meningococcalLOS may experience less severe disease than those whose initial response is anti-inflammatory. This observation suggests that the inflammatory response may be critical for restraining meningococcal growth. Attempts to identify disease- or severity-associated polymorphisms in cytokine genes have had inconclusive results, however.

## CLINICAL MANIFESTATIONS

**Upper Respiratory Tract Infections** Although many patients who develop meningococcal meningitis or meningococcemia report having had throat soreness or other upper respiratory symptoms during the preceding week, it is uncertain whether these symptoms are due to infection with meningococci. Meningococcal pharyngitis is

rarely diagnosed. Adult patients with *N. meningitidis* bacteremia more often have clinically apparent disease of the respiratory tract (pneumonia, sinusitis, tracheobronchitis, conjunctivitis) than do younger patients.

**Meningococcemia** Most patients with meningococcal disease have both meningococcemia *and* meningitis. These conditions have a wide clinical spectrum, with many overlapping features (Table 146-1).

Approximately 10 to 30% of patients with meningococcal disease have meningococcemia without clinically apparent meningitis. Although meningococcemia is occasionally transient and asymptomatic, in most individuals it is associated with fever, chills, nausea, vomiting, and myalgias. Prostration is common. The most distinctive feature is rash (Fig. 146-CD1). Erythematous macules rapidly become petechial and, in severe cases, purpuric. Although the lesions are typically found on the trunk and lower extremities, they may also occur on the face, arms, and mucous membranes. The petechiae may coalesce into hemorrhagic bullae or may undergo necrosis and ulcerate. Patients with severe coagulopathy may develop ischemic extremities or digits, often with a sharp line of demarcation between normal and ischemic tissue.

In many patients with fulminant meningococcemia, theCSF is normal and the CSF culture is negative. Indeed, the absence of meningitis in a patient with meningococcemia is a poor prognostic sign; it suggests that the bacteria have multiplied so rapidly in the blood that meningeal seeding has not yet had time to elicit inflammation in the CSF. Most of these patients also lack evidence of an acute-phase response; i.e., the erythrocyte sedimentation rate is normal, and the C-reactive protein concentration in blood is low.

The Waterhouse-Friderichsen syndrome is a dramatic example ofDIC-induced microthrombosis, hemorrhage, and tissue injury. Although overt adrenal failure is infrequently documented in patients with fulminant meningococcemia, patients may have partial adrenal insufficiency and be unable to mount the normal hypercortisolemic response to severe stress or cosyntropin stimulation. Almost all patients who die from fulminant meningococcemia have adrenal hemorrhages at autopsy.

Chronic meningococcemia is a rare syndrome of episodic fever, rash, and arthralgias that can last for weeks to months. The rash may be maculopapular; it is occasionally petechial. Splenomegaly may develop. If untreated or if treated with glucocorticoids, chronic meningococcemia may evolve into meningitis, fulminant meningococcemia, or (rarely) endocarditis.

**Meningitis (See also Chap. 372)** Patients with meningococcal meningitis have usually been sick for ³24 h before they seek medical attention. Common presenting symptoms include nausea and vomiting, headache, neck stiffness, lethargy, and confusion. The symptoms and signs of meningococcal meningitis cannot be distinguished from those elicited by other meningeal pathogens. Many patients with meningococcal meningitis have concurrent meningococcemia, however, and petechial or purpuric skin lesions may suggest the correct diagnosis.CSFfindings are consistent with those of purulent meningitis: hypoglycorrhachia, an elevated protein concentration, and a neutrophilic leukocytosis. A Gram's stain of CSF is usually positive (see "Diagnosis," below); when

this finding is unaccompanied by CSF leukocytosis, the prognosis for normal recovery is often poor.

**Other Manifestations** Arthritis occurs in ~10% of patients with meningococcal disease. When arthritis develops during the first few days of the patient's illness, it usually reflects direct meningococcal invasion of the joint. Arthritis that begins later in the course is thought to be due to immune complex deposition. Primary meningococcal pneumonia occurs principally in adults, often in military populations, and is most often due to serogroup Y. While meningococcal pericarditis is occasionally seen, endocarditis due to *N. meningitidis* is now exceedingly rare. Primary meningococcal conjunctivitis can be complicated by meningococcemia; systemic therapy is therefore warranted when this condition is diagnosed. Meningococcal urethritis has been reported in individuals who practice oral sex.

**Complications** Patients with meningococcal meningitis may develop cranial nerve palsies, cortical venous thrombophlebitis, and cerebral edema. In children subdural effusions may occur. Permanent sequelae can include mental retardation, deafness, and hemiparesis. The major long-term morbidity of fulminant meningococcemia is the loss of skin, limbs, or digits that results from ischemic necrosis and infarction.

## DIAGNOSIS

Few clinical clues help the physician distinguish the patient with early meningococcal disease from patients with other acute systemic infections. The most useful clinical finding is the petechial or purpuric rash (seePlate IID-44), but it must be differentiated from the petechial lesions seen with gonococcemia (seePlate IID-60), Rocky Mountain spotted fever (seePlate IID-45), hypersensitivity vasculitis (seePlate IIE-71), endemic typhus, and some viruses. In one case series, one-half of the adults with meningococcal bacteremia had neither meningitis nor a rash.

The definitive diagnosis is established by recovering *N. meningitidis*, its antigens, or its DNA from normally sterile body fluids, such as blood,CSF, or synovial fluid, or from skin lesions. Meningococci grow best on Mueller-Hinton or chocolate blood agar at 35°C in an atmosphere that contains 5 to 10% $CO_2$. Specimens should be plated without delay. *N. meningitidis* bacteria are oxidase-positive, gram-negative diplococci that typically utilize maltose and glucose.

A Gram's stain ofCSFreveals intra- or extracellular organisms in ~85% of patients with meningococcal meningitis. The latex agglutination test for meningococcal polysaccharides is somewhat less sensitive. Reports suggest that polymerase chain reaction amplification of DNA in buffy coat or CSF samples may be more sensitive than either of these tests, and, like the latex agglutination test, this method is not affected by prior antibiotic therapy.

Throat or nasopharyngeal specimens should be cultured on Thayer-Martin medium, which suppresses the competing oral flora. Throat or nasopharyngeal cultures are recommended only for research or epidemiologic purposes, since a positive result merely confirms the carrier state and does not establish the existence of systemic disease.

## TREATMENT

A third-generation cephalosporin, such as cefotaxime (2 g intravenously every 8 h) or ceftriaxone (1 g intravenously every 12 h), is preferred for initial therapy, as it may cover other bacteria (such as *Streptococcus pneumoniae* and *Haemophilus influenzae*) that can cause the same syndromes (Chap. 372). Penicillin G (4 million units intravenously every 4 h) remains an acceptable alternative in most countries; high-level penicillin resistance has been reported from Spain. In the patient who is allergic to b-lactam drugs, chloramphenicol (75 to 100 mg/kg every 6 h) is a suitable alternative; chloramphenicol-resistant meningococci have been reported from Vietnam and France, however. Although some cases of mild disease may be cured with only 2 days of treatment, most patients with meningococcal meningitis should be given antimicrobial therapy for at least 5 days. While glucocorticoid therapy for meningitis in adults is controversial, many experts administer dexamethasone, beginning if possible before antibiotic therapy is initiated (Chap. 372).

Patients with fulminant meningococcemia often experience diffuse leakage of fluid into extravascular spaces, shock, and multiple-organ dysfunction (Chaps. 38 and124). Myocardial depression may be prominent. Supportive therapy has never been studied in randomized, placebo-controlled trials. Standard measures include vigorous fluid resuscitation (often requiring several liters over the first 24 h), elective ventilation, and pressors (epinephrine or dopamine). Some authorities recommend early hemodialysis or hemofiltration. Fresh frozen plasma is often given to patients who are bleeding extensively or who have severely deranged clotting parameters. Many European experts prefer to administer antithrombin to such patients. Patients with fulminant meningococcemia in whom shock persists despite vigorous fluid resuscitation should receive supplemental glucocorticoid treatment (hydrocortisone, 1 mg/kg every 6 h) pending tests of adrenal reserve. Investigational drugs for fulminant meningococcemia include bactericidal permeability-increasing (BPI) protein -- a bactericidal neutrophil protein that binds and neutralizes meningococcalLOS -- as well as several anticoagulants (activated protein C, antithrombin, and tissue factor pathway inhibitor). In a recent clinical trial, recombinant BPI protein reduced long-term complications in children with fulminant meningococcemia without definitely reducing mortality.

## PROGNOSIS

When patients are first evaluated, the clinical features most strongly associated with a fatal outcome are shock, a purpuric or ecchymotic rash, a low or normal blood leukocyte count, an age ³60 years, and coma. The absence of meningitis, the presence of thrombocytopenia, low blood concentrations of antithrombin or proteins S and C, high blood levels ofPAI-1, and a low erythrocyte sedimentation rate (or C-reactive protein level) have also been associated with increased mortality from meningococcal disease. In contrast, having received antibiotics prior to hospital admission has been associated with lower mortality in some studies.

## PREVENTION

**Meningococcal Polysaccharide Vaccines** A single injection of quadrivalent

meningococcal polysaccharide vaccine (serogroups A, C, W-135, and Y) immunizes ~80 to 95% of immunocompetent adults. Children ³3 months of age can be vaccinated to prevent serogroup A disease, but multiple doses are required; the vaccine is otherwise ineffective in children<2 years old. The duration of vaccine-induced immunity in adults is probably <5 years. There is currently no vaccine for serogroup B; its polysaccharide is a sialic acid homopolymer that is poorly immunogenic in humans. In addition to individuals with late-complement-component or properdin deficiency, persons with sickle cell anemia, asplenia, or splenectomy should receive the quadrivalent vaccine. Vaccination is also recommended for military recruits and for individuals traveling to sub-Saharan Africa during the dry months (June to December) or to other areas with epidemic meningococcal disease. Some authorities recommend vaccination of incoming college freshmen who will live in dormitories. In general, the vaccine should be given only to persons³2 years of age. Investigational polysaccharide-protein conjugate meningococcal vaccines appear promising; a serogroup C conjugate vaccine was licensed for use in the United Kingdom in 1999.

Screening tests for late-complement-component deficiency should be done in family members of patients who have a family history of meningococcal disease, in patients who have a recurrence, in those whose first case occurs at³15 years of age, and in those with cases caused by serogroups other than A, B, or C.

**Antimicrobial Chemoprophylaxis** The attack rate for meningococcal disease among household contacts of cases is ~500-fold greater than that in the population as a whole. Close contacts of cases should receive chemoprophylaxis with rifampin (adult dosage, 600 mg orally every 12 h for four doses), ciprofloxacin (a single oral dose of 500 mg), or ofloxacin (a single oral dose of 400 mg). A single intramuscular injection of ceftriaxone (250 mg) is also effective. Close contacts include persons who live in the same household, day-care center contacts, and anyone directly exposed to the patient's oral secretions. Casual contacts are not at increased risk. Chemoprophylaxis should be administered as soon as possible after the case is identified.

**Isolation Precautions** The Centers for Disease Control and Prevention recommend that patients with meningococcal disease who are hospitalized be placed in respiratory isolation for the first 24 h.

**Outbreak Control** An organization- or community-based outbreak of meningococcal disease is defined as the occurrence of three or more cases within £3 months in persons who have a common affiliation or reside in the same area but who are not close contacts of one another; in addition, the primary disease attack rate must exceed 10 cases per 100,000 persons, and the case strains of *N. meningitidis* must be of the same molecular type. Mass vaccination should be considered when such outbreaks occur, and mass chemoprophylaxis may be used to control school- or other institution-based outbreaks. Consultation with public health authorities is recommended when such campaigns are contemplated.

(Bibliography omitted in Palm version)

Back to Table of Contents

## 147. GONOCOCCAL INFECTIONS - *Sanjay Ram*, *Peter A. Rice*

### DEFINITION

Gonorrhea is a sexually transmitted infection of epithelium and commonly manifests as cervicitis, urethritis, proctitis, and conjunctivitis. If untreated, infections at these sites can lead to local complications such as endometritis, salpingitis, tuboovarian abscess, bartholinitis, peritonitis, and perihepatitis in the female; periurethritis and epididymitis in the male; and ophthalmia neonatorum in the newborn. Disseminated gonococcemia is an uncommon event whose manifestations include skin lesions, tenosynovitis, arthritis, and (in rare cases) endocarditis or meningitis.

*Neisseria gonorrhoeae* is a gram-negative, nonmotile, non-spore-forming organism that grows in pairs (diplococci). Each individual organism is shaped like a coffee bean, with adjacent concave sides seen on Gram's stain. Gonococci, like all other *Neisseria* spp., are oxidase positive. They are distinguished from other *Neisseria* by their ability to grow on selective media and to utilize glucose but not maltose, sucrose, or lactose.

### EPIDEMIOLOGY

The incidence of gonorrhea has declined significantly in the United States, but there are still ~315,000 newly reported cases each year. Gonorrhea remains a major public health problem worldwide, is a significant cause of morbidity in developing countries, and may play a role in enhancing transmission of HIV.

Gonorrhea predominantly affects young, nonwhite, unmarried, less educated members of urban populations. The number of reported cases probably represents half of the true number of cases -- a discrepancy resulting from underreporting, self-treatment, and nonspecific treatment without a culture-proven diagnosis. The number of reported cases of gonorrhea in the United States rose from ~250,000 in the early 1960s to a high of 1.01 million in 1978. The peak recorded incidence of gonorrhea in modern times was noted in 1975, with 468 cases per 100,000 population in the United States. This peak was attributable to the interaction of several variables, including improved accuracy of diagnosis, changes in patterns of contraceptive use, and changes in sexual behavior. The incidence of the disease has since gradually declined and is currently estimated at 120 cases per 100,000, a figure that is still the highest among industrialized countries. A further decline in the overall incidence of gonorrhea in the United States over the past decade may reflect increased condom use resulting from public health efforts to curtail HIV transmission. Presently, the attack rate in the United States is highest in the 20- to 24-year age group, in which 75% of all cases occur. With adjustment for sexual experience, the risk is highest among sexually active 15- to 19-year-old women. In terms of ethnicity, rates are highest among African-Americans and lowest among persons of Asian or Pacific Island descent.

The highest incidence of gonorrhea occurs in developing countries. The exact incidence of any of the sexually transmitted diseases (STDs) is difficult to ascertain in developing countries because of limited surveillance and variable diagnostic criteria. For example, in Kenya, it was estimated in 1987 that 10% of all live births were adversely affected by STDs, and gonococcal ophthalmia neonatorum reportedly affected 4% of all live-born

infants. The median prevalence of gonorrhea in unselected populations of pregnant women has been estimated at 10% in Africa, 5% in Latin America, and 4% in Asia. Studies in Africa have clearly demonstrated that nonulcerative STDs such as gonorrhea are an independent risk factor for the transmission of HIV (Chap. 309).

Gonorrhea is transmitted from males to females more efficiently than in the opposite direction. The rate of transmission to a woman following a single unprotected sexual encounter with an infected man is on the order of 40 to 60%. Oropharyngeal gonorrhea occurs in ~20% of women who practice fellatio with infected partners. Transmission in either direction by cunnilingus is rare.

There exists in any population a small minority of individuals who have high rates of new partner acquisition. These "core-group members" or "high-frequency transmitters" are vital in sustainingSTDtransmission at the population level. Another instrumental factor in sustaining gonorrhea in the population is the large number of infected individuals who are asymptomatic or have minor symptoms that are ignored. These persons, unlike symptomatic individuals, do not cease sexual activity and therefore continue to transmit the disease. This situation underscores the importance of contact tracing and empirical treatment of sex partners of index cases.

## PATHOGENESIS AND IMMUNOLOGY

### Outer-Membrane Proteins

*Pili* Fresh clinical isolates of *N. gonorrhoeae* initially form piliated (fimbriated) colonies distinguishable on translucent agar. Pilus expression is rapidly switched off with unselected subculture because of rearrangements in pilus genes. This change is a basis for phase variation of gonococci. Piliated strains adhere better to cells derived from human mucosal surfaces and are more virulent in organ culture models and human inoculation experiments than nonpiliated variants. In a fallopian tube explant model, pili mediate gonococcal attachment to nonciliated columnar epithelial cells. This event initiates gonococcal phagocytosis and transport through these cells to intercellular spaces near the basement membrane or directly into the subepithelial tissue. Damage to nearby ciliated columnar epithelial cells, which is caused by the release of cytokines, results in loss of cilia and sloughing of ciliated cells and diminishes the integrity of the fallopian tube. Nonpiliated gonococci cause epithelial damage at a much slower rate. CD46 (membrane cofactor protein) is present on urogenital epithelial cells in both men and women and has been determined to be a receptor for PilC; this subunit is located at the tip of the pilus molecule and is critical in mediating adherence. Pili are also essential for genetic competence and transformation of *N. gonorrhoeae*, which permits horizontal transfer of genetic material between different gonococcal lineages in vivo.

*Opacity-associated protein* Another gonococcal surface protein that is important in adherence to epithelial cells is opacity-associated protein (Opa, formerly called protein II). Opa contributes to intergonococcal adhesion, which is responsible for the opaque nature of gonococcal colonies on translucent agar and the organism's adherence to a variety of eukaryotic cells, including polymorphonuclear leukocytes (PMNs). Certain Opa variants promote invasion of epithelial cells, and this effect has been linked with the ability of Opa to bind vitronectin, glycosaminoglycans, and several members of the

carcinoembryonic antigen family (CD66). Each strain of *N. gonorrhoeae* possesses as many as 11 different *opa* genes, but usually only up to 3 types are expressed at any given time. Isolates from normally sterile sites such as the fallopian tube and synovial fluid usually fail to express Opa, while isolates from mucosal sites usually form opaque colonies. Female commercial sex workers with antibodies to Opa may be less likely to develop pelvic inflammatory disease (PID) than women without such antibodies.

*Porin* Porin (previously designated protein I) is the most abundant gonococcal surface protein, accounting for >50% of the organism's total outer-membrane protein. Porin molecules exist as trimers that provide anion aqueous channels through the otherwise hydrophobic outer membrane. Porin shows stable interstrain antigenic variation and forms the basis for gonococcal serotyping. Two main serotypes have been identified: Por1A strains are often associated with disseminated gonococcal infection (DGI), while Por1B strains usually cause local genital infections only. DGI strains are generally resistant to the killing action of normal human serum, do not incite a significant local inflammatory response, and therefore may not cause symptoms at genital sites. These characteristics may be related to the ability of Por1A strains to bind to complement-downregulatory molecules, resulting in a diminished inflammatory response. Porin can translocate to the cytoplasmic membrane of host cells -- a process that could initiate gonococcal endocytosis and invasion. In addition, porin is an immunologic target of bactericidal and opsonophagocytic antibodies that may arise in response to immune stimulation resulting from infection or immunization with porin-containing vaccine candidates.

*Other outer-membrane proteins* Other notable outer-membrane proteins include H.8, a lipoprotein that is present on the surface of all gonococcal strains in high concentration and is an excellent target for antibody-based diagnostic testing, as well as transferrin-binding proteins (Tbp1 and Tbp2) and lactoferrin-binding protein, which are required for scavenging iron from transferrin and lactoferrin in vivo. Transferrin and iron have been shown to increase attachment of iron-deprived *N. gonorrhoeae* to human endometrial cells. Gonococci deficient in transferrin- and lactoferrin-binding proteins cannot establish infection in male volunteers. IgA1 protease is produced by *N. gonorrhoeae* and may protect the organism from the action of mucosal IgA.

**Lipooligosaccharide** Gonococcal lipooligosaccharide (LOS) consists of a lipid A and a core oligosaccharide that lacks the repeating O-carbohydrate antigenic side chain seen in other gram-negative bacteria (Chap. 120). Gonococcal LOS possesses marked endotoxic activity and contributes to the local cytotoxic effect in the fallopian tube model. LOS core sugars undergo a high degree of antigenic variation under different conditions of growth; this variation reflects genetic regulation and expression of glycotransferase genes that dictate the carbohydrate structure of LOS. These phenotypic changes may affect interactions of *N. gonorrhoeae* with elements of the humoral immune system (antibodies and complement) and may also influence direct binding of organisms to both professional and nonprofessional phagocytes (epithelial cells). For example, gonococci that are sialylated at their LOS sites bind complement factor H and downregulate the alternative pathway of complement. LOS sialylation may also mask bactericidal antibody-binding epitopes on LOS and porin and may decrease opsonophagocytosis and inhibit the oxidative burst inPMNs. While sialylation of LOS confers on the bacteria the ability to attenuate the inflammatory response and evade the innate immune system,

experiments in male volunteers suggest that sialylated gonococci may be less capable of establishing infection than their unsialylated counterparts. This difference could be explained by the observation that the unsialylated terminal lactosamine residue of LOS binds to an asialoglycoprotein receptor on epithelial cells that would otherwise facilitate binding and subsequent gonococcal invasion of these cells.

**Host Factors** In addition to gonococcal structures that interact with epithelial cells, host factors seem to be important in mediating entry of gonococci into nonphagocytic cells. Activation of phosphatidylcholine-specific phospholipase C and acidic sphingomyelinase by *N. gonorrhoeae*, which results in the release of diacylglycerol and ceramide, is an essential requirement for the entry of *N. gonorrhoeae* into epithelial cells. Ceramide accumulation within cells leads to apoptosis, which may disrupt epithelial integrity and facilitate entry of gonococci into subepithelial tissue. Release of chemotactic factors as a result of complement activation contributes to inflammation, as does the toxic effect of LOSin provoking the release of inflammatory cytokines.

The importance of humoral immunity in host defenses against neisserial infections is best illustrated by the predisposition of persons deficient in terminal complement components (C5 through C9) to recurrent bacteremic gonococcal infections and to recurrent meningococcal meningitis or meningococcemia. Gonococcal porin induces T cell proliferative responses in persons with urogenital gonococcal disease. A significant increase in porin-specific interleukin (IL) 4-producing CD4+ as well as CD8+ lymphocytes is seen in individuals with mucosal gonococcal disease. A portion of these lymphocytes that show a porin-specific $T_H2$-type response could traffic to mucosal surfaces and play a role in immune protection against the disease. Few data clearly indicate that protective immunity is acquired from a previous gonococcal infection, although bactericidal and opsonophagocytic antibodies to porin andLOS may offer partial protection. On the other hand, women who are infected and acquire high levels of antibody to another outer-membrane protein, Rmp (reduction modifiable protein, formerly called protein III), may be especially likely to become reinfected with *N. gonorrhoeae* because Rmp antibodies block the effect of bactericidal antibodies to porin and LOS. Rmp shows little, if any, interstrain antigenic variation; therefore, Rmp antibodies potentially may block antibody-mediated killing of all gonococci. The mechanism of blocking has not been fully characterized, but Rmp antibodies noncompetitively inhibit binding of porin and LOS antibodies because of the proximity of these structures in the gonococcal outer membrane. Less well understood is how blocking antibody may divert complement binding to the gonococcal surface or otherwise hasten inactivation of complement. In male volunteers who have no history of gonorrhea, the net effect of these events may influence the outcome of experimental challenge with *N. gonorrhoeae*. Because Rmp bears extensive homology to enterobacterial OmpA and meningococcal class 4 proteins, it is possible that these blocking antibodies result from prior exposure to cross-reacting proteins from these species and also play a role in first-time infection with *N. gonorrhoeae*.

## CLINICAL MANIFESTATIONS

**Gonococcal Infection in Males** Acute urethritis is the most common clinical manifestation of gonorrhea in males. The usual incubation period following exposure is 2 to 7 days, although the interval can be longer and some men remain asymptomatic.

Strains of the Por1A serotype, with nutritional requirements for arginine, hypoxanthine, and uracil (i.e., the AHU auxotype), tend to cause a greater proportion of cases of mild and asymptomatic urethritis than Por1B strains. Urethral discharge (Fig. 147-CD1) and dysuria, usually without urinary frequency or urgency, are the major symptoms. The discharge initially is scant and mucoid but becomes profuse and purulent within a day or two. The clinical manifestations of gonococcal urethritis are usually more severe and overt than those of nongonococcal urethritis, including urethritis caused by *Chlamydia trachomatis* (Chap. 179); however, exceptions are common, and it is often impossible to differentiate the causes of urethritis on clinical grounds alone. Most symptomatic males seek treatment and cease to be infectious. The remaining men, who are largely asymptomatic, accumulate in number over time and constitute about two-thirds of all infected men at any point in time. Together with men incubating the organism (who shed the organism but are asymptomatic), they serve as the source of spread of infection. Prior to the antibiotic era, symptoms of urethritis persisted for about 8 weeks. Epididymitis is now an uncommon complication, and gonococcal prostatitis occurs rarely, if at all. Other unusual local complications of gonococcal urethritis include edema of the penis due to dorsal lymphangitis or thrombophlebitis, submucous inflammatory "soft" infiltration of the urethral wall, periurethral abscess or fistulae, inflammation or abscess of Cowper's gland, and seminal vesiculitis. Balanitis may develop in uncircumcised men. After a decline in gonococcal infections among homosexual men early in the era of AIDS, a disturbing increase in gonorrhea was observed among young homosexual men in the 1990s, probably related to decreased condom use. The clinical features of anorectal and pharyngeal gonorrhea are discussed below.

**Gonococcal Infections in Females**

*Gonococcal cervicitis* Mucopurulent cervicitis is the most commonSTDdiagnosis in American women and may be caused by *N. gonorrhoeae*, *C. trachomatis*, and other organisms. Cervicitis may coexist with candidal or trichomonal vaginitis. *N. gonorrhoeae* primarily infects the cervical os but can also infect more peripheral areas of the cervix where columnar epithelium meets stratified squamous epithelium. Except in rare instances, the vaginal mucosa, which is lined by stratified squamous epithelium, does not become infected. Bartholin's glands occasionally become infected.

Women infected with *N. gonorrhoeae* usually develop symptoms. However, the women who either remain asymptomatic or have only minor symptoms may delay in seeking medical attention. Increased vaginal discharge and dysuria (often without urgency or frequency) are the most common symptoms. Although the incubation period of gonorrhea is less well defined in women than in men, symptoms usually develop within 10 days of infection and are more acute and intense than those of chlamydial cervicitis.

The physical examination may reveal a mucopurulent discharge (mucopus) issuing from the cervical os. The examiner may check for mucopurulent discharge by swabbing a sample of mucus from the endocervix and observing its color against the white background of the swab; yellow or green mucus suggests mucopus. However, only 35% of women with gonococcal cervicitis actually have a mucopurulent discharge defined by these criteria. Since Gram's stain is not sensitive for the diagnosis of gonorrhea in women, specimens should be submitted for culture or a nonculture assay (see below). Edematous and friable cervical ectopy as well as endocervical bleeding induced by

gentle swabbing are more often seen in chlamydial infection.

*N. gonorrhoeae* may be recovered from the urethra and rectum of women with cervicitis, but these are rarely the sole infected sites. Urethritis in women may produce symptoms of internal dysuria, which is often attributed to "cystitis." Pyuria in the absence of bacteriuria seen on Gram's stain of unspun urine, accompanied by urine cultures that fail to yield>$10^5$colonies of bacteria usually associated with urinary tract infection, signifies the possibility of urethritis due to *C. trachomatis*. Urethral infection with *N. gonorrhoeae* may also occur in this context, but in this instance urethral cultures will usually be positive. Compression of the urethra through the anterior vaginal wall against the symphysis pubis may express urethral exudate.

*Complications of gonococcal cervicitis* Gonococcal infection may extend deep enough to produce dyspareunia and lower abdominal or back pain. In such cases, it is imperative to consider a diagnosis ofPID and to administer treatment for that disease (Chap. 133). Ascending infection of the genital tract follows ~20% of cases of gonococcal cervicitis and may result in acute endometritis accompanied by abnormal menstrual bleeding, midline lower abdominal pain and tenderness, and dyspareunia. Spread to the fallopian tubes results in acute salpingitis, whose symptoms may be accompanied by signs of cervical motion tenderness and abnormal adnexal mass on pelvic examination. Patients may be febrile, and leukocytosis and an elevated erythrocyte sedimentation rate or C-reactive protein level may be detected. Co-infection with *C. trachomatis* may increase the risk of PID, which is the clinical counterpart of endometritis and salpingitis. Tubal scarring leading to infertility is the most devastating sequela of salpingitis; the increased risk of ectopic pregnancy is also significant. Prompt and appropriate antibiotic therapy for gonococcal salpingitis (prior to the development of an adnexal mass) can prevent tubal infertility in nearly all cases. Bilateral tubal damage occurs in ~20% of women with an adnexal mass. More than half of women with tubal infertility give no history of PID. These women with "silent salpingitis" may report abdominal or pelvic discomfort (such as dysmenorrhea or dyspareunia) that may be attributed to other diagnoses (such as endometriosis). Spread of infection to the pelvis may result in pelvic peritonitis characterized by nausea and vomiting. Spread of gonococci -- or, more commonly, of chlamydiae -- via the peritoneal cavity to the upper abdomen may cause perihepatitis (Fitz-Hugh-Curtis syndrome;Chap. 133).

*Gonococcal vaginitis* The vaginal mucosa of healthy women is lined by stratified squamous epithelium and is usually not infected by *N. gonorrhoeae*. However, gonococcal vaginitis can occur in anestrogenic women (e.g., prepubertal girls and postmenopausal women), in whom the vaginal stratified squamous epithelial layers are often thinned down to the basilar layer, which can be infected by *N. gonorrhoeae*. The intense inflammation of the vagina makes the physical (speculum and bimanual) examination extremely painful. The vaginal mucosa is red and edematous, and an abundant purulent discharge is present. Infection in the urethra and in Skene's and Bartholin's glands often accompanies gonococcal vaginitis. Inflamed cervical erosion or abscesses in nabothian cysts may also occur. Coexisting cervicitis may result in pus in the cervical os.

**Anorectal Gonorrhea** Because the female anatomy permits the spread of cervical exudate to the rectum, *N. gonorrhoeae* is sometimes recovered from the rectum of

women with uncomplicated gonococcal cervicitis. The rectum is the sole site of infection in only 5% of women with gonorrhea. Such women are usually asymptomatic but occasionally have acute proctitis manifested by anorectal pain or pruritus, tenesmus, purulent rectal discharge, and rectal bleeding. Among homosexual men, the frequency of gonococcal infection, including rectal infection, fell by³90% throughout the United States in the early 1980s, but a resurgence of gonorrhea among homosexual men was documented in several cities during the 1990s. Gonococcal isolates from the rectum of homosexual men tend to be more resistant than other gonococcal isolates to antimicrobials. Gonococci with multidrug resistance (*mtr*) are more resistant to bile salts and fatty acids in feces and thus are found with increased frequency in homosexual men. The *mtr* mutation involves a DNA-binding protein and results in the derepression of genes encoding an efflux mechanism of resistance. This situation may have been responsible for higher rates of treatment failure for rectal gonorrhea with older regimens consisting of penicillin or tetracyclines.

**Pharyngeal Gonorrhea** Pharyngeal gonorrhea is usually mild or asymptomatic, although symptomatic pharyngitis does occasionally occur with cervical lymphadenitis. The mode of acquisition is oral-genital sexual exposure, with fellatio being a more efficient means of transmission than cunnilingus. Most cases resolve spontaneously, and transmission from the pharynx to sexual contacts is rare. Pharyngeal infection almost always coexists with genital infection. Swabs from the pharynx should be plated directly onto gonococcal selective media. Because pharyngeal colonization with *N. meningitidis* needs to be differentiated from that with other *Neisseria* species, the diagnosis of pharyngeal gonorrhea is more expensive and difficult than that of anogenital gonorrhea.

**Ocular Gonorrhea in Adults** Ocular gonorrhea in an adult usually results from autoinoculation from an infected genital site. As in genital infection, the manifestations range from severe to occasionally mild or asymptomatic disease. The variability in clinical manifestations may result from differences in the ability of the infecting strain to elicit an inflammatory response.

Infection may result in a markedly swollen eyelid, severe hyperemia and chemosis, and a profuse purulent discharge (Fig. 147-CD2). The massively inflamed conjunctiva may be draped over the cornea and limbus. Lytic enzymes from the infiltratingPMNsoccasionally cause corneal ulceration and rarely cause perforation.

Prompt recognition and treatment of this condition are of paramount importance. Gram's stain and culture of the purulent discharge establish the diagnosis. Genital cultures should also be performed.

**Gonorrhea in Pregnant Women, Neonates, and Children** Gonorrhea in pregnancy can have serious consequences for both the mother and the infant. Therefore, early detection and eradication of the disease in the mother are extremely important. Recognition of gonorrhea early in pregnancy also identifies a population at risk for otherSTDs, particularly *Chlamydia* infection and syphilis. These women should be monitored closely for these infections throughout pregnancy. The incidence of gonorrhea in pregnancy ranges from rare to ~10%, depending upon the population surveyed. Salpingitis andPID can occur during the first trimester and are associated with

a high rate of fetal loss. In the second and third trimesters, the relative impermeability of the cervical mucus (under the influence of progesterone) and the obliteration of the intrauterine cavity (resulting from the attachment of the chorion to the endometrial decidua by around the twelfth week of gestation) pose physical barriers that usually prevent ascending infection. Pharyngeal infection, most often asymptomatic, may be more common during pregnancy because of altered sexual practices. Acquisition of gonococcal infection late in pregnancy can adversely affect labor and delivery as well as the well-being of the fetus. Prolonged rupture of the membranes, premature delivery, chorioamnionitis, funisitis (infection of the umbilical cord stump), and sepsis in the infant (with *N. gonorrhoeae* detected in the gastric aspirate of the newborn during delivery) are common complications of maternal gonococcal infection at term. Hazards to the fetus include spontaneous abortion, perinatal death, premature delivery, perinatal distress, and premature rupture of membranes. Other microorganisms and conditions, including *Mycoplasma hominis*, *Ureaplasma urealyticum*, *C. trachomatis*, and bacterial vaginosis, have been associated with similar complications.

The most common form of gonorrhea in neonates is *ophthalmia neonatorum*, which results from exposure to infected cervical secretions during parturition. Ocular neonatal instillation of a prophylactic agent (e.g., 1% silver nitrate eyedrops or ophthalmic preparations containing erythromycin or tetracycline) is a cost-effective measure for the prevention of ophthalmia neonatorum but is not effective for its treatment, which requires systemic antibiotics. The clinical manifestations are acute and begin 2 to 5 days after birth. A small inoculum of organisms, low virulence of the infecting strain, or partial suppression by ophthalmic prophylaxis can result in a more indolent course. Therefore, gonococcal infection must be ruled out by culture in every case of conjunctivitis in infants. An initial nonspecific conjunctivitis with a serosanguineous discharge is followed by tense edema of both eyelids, chemosis, and a profuse, thick, purulent discharge. Corneal ulcerations that result in nebulae or perforation may lead to anterior synechiae, anterior staphyloma, panophthalmitis, and blindness. Infections described at other mucosal sites in infants, including vaginitis, rhinitis, and anorectal infection, are likely to be asymptomatic. Pharyngeal colonization has been demonstrated in 35% of infants with gonococcal ophthalmia, and coughing is the most prominent symptom in these cases. Septic arthritis is the most common manifestation of systemic gonococcal infection in the newborn. The primary focus ofDGI in most of these cases is uncertain. The onset usually comes at 3 to 21 days of age, and polyarticular involvement is common. Sepsis, meningitis, and pneumonia are seen in rare instances.

AnySTD in children beyond the neonatal period raises the possibility of sexual abuse. In most cases of abuse, the perpetrator is a male assailant known to the child. Gonococcal vulvovaginitis is the most common manifestation of gonococcal infection in children beyond infancy. Anorectal and pharyngeal infections are common in these children and are frequently asymptomatic. The urethra, Bartholin's and Skene's glands, and the upper genital tract are rarely involved. All children with gonococcal infection should also be evaluated for *Chlamydia* infection, syphilis, and possibly HIV infection. All cases of suspected and confirmed child abuse should be reported to the appropriate social service agency in the county where the child resides.

**Disseminated Gonococcal Infection** DGIresults from gonococcal bacteremia. In the 1970s, DGI occurred in ~0.5% to 3% of persons with untreated gonococcal mucosal

infection. The lower incidence at present is probably attributable to a decline in the prevalence of particular strains that are likely to disseminate. DGI strains resist the bactericidal action of human serum and generally do not incite inflammation at genital sites, probably because of limited generation of chemotactic factors. These strains are often of the Por1A serotype, are highly susceptible to penicillin, and have special nutritional requirements (i.e., the AHU auxotype). Menstruation is a risk factor for dissemination, and approximately two-thirds of cases of DGI are in women. In about half of affected women, symptoms of DGI begin within 7 days of onset of menses. Complement deficiencies, especially of the components involved in the assembly of the membrane attack complex (C5 through C9), predispose to neisserial bacteremia. Up to 13% of patients with DGI have complement deficiencies, and persons with more than one episode of DGI should be screened with an assay for total hemolytic complement activity.

The clinical manifestations ofDGI have sometimes been classified into two stages: a bacteremic stage and a joint-localized stage with suppurative arthritis. A clear-cut progression usually is not evident. Patients in the bacteremic stage have higher temperatures, and their fever is more frequently accompanied by chills. Painful joints are common and often occur in conjunction with tenosynovitis and skin lesions.

Polyarthralgias usually include the knees, elbows, and more distal joints; the axial skeleton is generally spared. Skin lesions are seen in ~75% of patients and include papules and pustules, often with a hemorrhagic component (seePlate IID-60;Fig. 147-CD3). These lesions are usually on the extremities and number between 5 and 40. Frank arthritis, when it develops, involves one or two joints, most often (in decreasing order of frequency) the knees, wrists, ankles, and elbows. The occurrence of arthritis in the absence of signs and symptoms of the bacteremic stage has led to the suggestion that these are separate syndromes. Other joints, such as the small joints of the hands and feet and the sternoclavicular and temporomandibular joints, are occasionally involved. Most patients who develop gonococcal septic arthritis do so without prior polyarthralgias or skin lesions; in the absence of symptomatic genital infection, this disease cannot be distinguished from septic arthritis caused by other pathogens. Rarely, osteomyelitis complicates septic arthritis involving small joints.

Although it has been postulated that the initial arthritis and skin lesions are due to direct tissue invasion by *N. gonorrhoeae*, the organism has been recovered from fewer than 5% of skin lesions cultured. This low isolation rate has been attributed to either a small inoculum of infecting organisms or the fastidious growth requirements of *N. gonorrhoeae* strains that disseminate. Gonococcal antigens have been identified in "sterile" skin lesions by immunofluorescent staining techniques. There is also evidence that immune-mediated or hypersensitivity phenomena caused by gonococcal antigens account for skin lesions. Other manifestations of noninfectious dermatitis, such as nodular lesions, urticaria, and erythema multiforme, have been described. Gonococcal endocarditis, although rare today, was relatively common in the preantibiotic era, causing about one-quarter of reported cases of endocarditis. Another unusual complication ofDGI is meningitis.

**Gonococcal Infection in HIV-Infected Persons** The association between gonorrhea and the acquisition of HIV has been demonstrated in several well-controlled studies,

mainly in Kenya and Zaire. The nonulcerativeSTDsenhance the transmission of HIV by three- to fivefold, possibly because of increased viral shedding in persons with urethritis or cervicitis (Chap. 309). HIV has been detected by polymerase chain reaction (PCR) more commonly in ejaculates from HIV-positive men with gonococcal urethritis than in those from HIV-positive men with nongonococcal urethritis. PCR positivity diminishes by twofold following appropriate therapy for urethritis. Not only does gonorrhea enhance the transmission of HIV; it may also increase the individual's risk for acquisition of HIV. A proposed mechanism is the significantly greater number of CD4+ lymphocytes and dendritic cells that can be infected by HIV in endocervical secretions of women with nonulcerative STDs than in those of women with ulcerative STDs.

## DIFFERENTIAL DIAGNOSIS

The clinical features of uncomplicated gonococcal infections closely resemble those of genital infections caused by *C. trachomatis*. Although the symptoms produced by chlamydial infections tend to be milder, the two infections are often indistinguishable on clinical grounds alone. Co-infection with *N. gonorrhoeae* and *C. trachomatis* is seen in up to 40% of cases. The differential diagnosis of urethritis, epididymitis, and proctitis in men, of cervicitis in women, and of vaginitis in prepubertal girls is discussed inChap. 132; that ofPID inChap. 133; and that of acute arthritis in young adults in Chap. 323. The differential diagnosis of the bacteremic stage ofDGIincludes acute rheumatoid arthritis, sarcoidosis, erythema nodosum, drug-induced arthritis, and viral infections (e.g., hepatitis B and acute HIV infection).

## LABORATORY DIAGNOSIS

A rapid diagnosis of gonococcal infection in men may be obtained by Gram's staining of urethral exudates (Fig. 147-CD4). The detection of gram-negative intracellular diplococci (GNID) is usually highly specific and sensitive in diagnosing gonococcal urethritis in symptomatic males but is only ~50% sensitive in diagnosing gonococcal cervicitis. Samples should be collected with Dacron or rayon swabs. Part of the sample should be inoculated onto a plate of modified Thayer-Martin or other gonococcal selective medium for culture. It is important to process all samples immediately because gonococci do not tolerate drying. If plates cannot be incubated immediately, they can be held safely for several hours at room temperature in candle extinction jars prior to incubation. If processing is to occur within 6 h, transport of specimens may be facilitated by the use of nonnutritive swab transport systems such as Stuart or Amies medium. For longer holding periods (e.g., when specimens for culture are to be mailed), culture media with self-contained $CO_2$-generating systems (such as the JEMBEC or Gono-Pak systems) may be used. Specimens should also be obtained for the diagnosis of chlamydial infection.

PMNsare often seen in the endocervix on a Gram's stain, and an abnormally increased number (³30 PMNs per field in five 1000´ oil-immersion fields) establishes the presence of an inflammatory discharge (mucopurulent cervicitis). Unfortunately, the presence or absence ofGNID in cervical smears does not accurately predict which patients have gonorrhea, and the diagnosis in this setting should be made by culture. The sensitivity of a single endocervical culture is ~80 to 90%, with the precise figure depending on the quality of the medium and the adequacy of the clinical specimen. The yield can be

enhanced by culture of a second cervical specimen. If a history of rectal sex is elicited, a rectal wall swab (uncontaminated with feces) should be cultured. A presumptive diagnosis of gonorrhea cannot be made on the basis of gram-negative diplococci in smears from the pharynx, where other *Neisseria* species are components of the normal flora.

Nucleic acid probe tests are now widely used for the direct detection of *N. gonorrhoeae* in urogenital specimens. A common assay employs a nonisotopic chemiluminescent DNA probe that hybridizes specifically with gonococcal 16S ribosomal RNA. Studies assessing the utility of the nucleic acid probe system in high-risk outpatients undergoing screening forSTDshave revealed that it is at least as sensitive as conventional culture techniques and may be a cost-effective alternative to culture, especially in high-risk males. A disadvantage of non-culture-based assays in general is that specimens submitted in probe-transport systems cannot be cultured subsequently. Therefore, a culture-confirmatory test is not possible, and formal antimicrobial susceptibility testing, if needed, cannot be performed. Low-cost point-of-care tests are under development for use in resource-poor settings, where specific diagnosis often gives way to syndromic management. DNA amplification techniques such asPCR may eventually prove to be equivalent to or more sensitive than culture methods.

Because of the legal implications, gonococcal infection in children must be diagnosed only with standard culture systems. Nonculture tests for gonococcal infection should not be used alone and have not been approved by the U.S. Food and Drug Administration for use with specimens obtained from the genital tract, pharynx, and rectum of infected children. Cultures should be obtained from the pharynx and anus of both girls and boys, the vagina of girls, and the urethra of boys. Cervical specimens are not recommended for prepubertal girls. For boys with a urethral discharge, a meatal specimen of the discharge is adequate for culture. Presumptive colonies of *N. gonorrhoeae* should be identified definitively by at least two independent methods (e.g., biochemical, enzyme substrate, or serologic).

Blood should be cultured in suspected cases ofDGI. The use of Isolator blood culture tubes may enhance the yield. The probability of positive blood cultures decreases after 48 h of illness. Synovial fluid should be inoculated into blood culture broth medium and plated onto chocolate agar rather than selective medium because this fluid is not likely to be contaminated with commensal bacteria. Gonococci are infrequently recovered from early joint effusions containing <20,000 leukocytes/uL but may be recovered from effusions containing >80,000 leukocytes/uL. The organisms are seldom recovered from blood and synovial fluid of the same patient.

## TREATMENT

It is no surprise that *N. gonorrhoeae*, with its remarkable capacity to alter its antigenic structure and adapt to changes in the microenvironment, has become resistant to numerous antibiotics. The first effective agents against gonorrhea were the sulfonamides, which were introduced in the 1930s. Within a decade, antibiotic resistance emerged, resulting in treatment failures in one-third of patients. Penicillin was then employed as the drug of choice for the treatment of gonorrhea. By 1965, 42% of gonococcal isolates had developed low-level resistance to penicillin G. To prevent

treatment failures, the Centers for Disease Control and Prevention (CDC) at that time recommended doubling the dose of penicillin for the treatment of gonorrhea. Resistance due to the production of penicillinase arose later.

Gonococci become fully resistant to antibiotics either by chromosomal mutations or by acquisition of R factors (plasmids). Two types of chromosomal mutations have been described. The first type, which is drug specific, is a single-step mutation leading to high-level resistance. The second type involves mutations at several chromosomal loci that combine to determine the level as well as the pattern of resistance. Strains with mutations in chromosomal genes were first observed in the late 1950s. As recently as 1997, strains with chromosomal resistance (CMRNG) accounted for resistance to penicillin, tetracycline, or both in ~20% of strains surveyed in the United States.

b-Lactamase (penicillinase)-producing strains of *N. gonorrhoeae* (PPNG) carrying plasmids with the $Pc_r$determinant were seen almost simultaneously in the United States, England, western Africa, and the Philippines in the late 1970s. PPNG strains have since spread worldwide and by the early 1980s accounted for>50% of all gonococcal isolates in some parts of the developing world. The average prevalence of PPNG in the United States dropped by two-thirds after most penicillin use was discontinued and is now on the order of 4%, with higher rates reported from certain areas. *N. gonorrhoeae* strains with plasmid-borne tetracycline resistance (TRNG) can mobilize some b-lactamase plasmids, and PPNG and TRNG occur together, sometimes along with CMRNG. Penicillin, ampicillin, and tetracycline are no longer reliable agents for the treatment of gonorrhea and should not be used. Third-generation cephalosporins have remained highly effective as single-dose therapy for gonorrhea. Even though the minimal inhibitory concentrations (MICs) of ceftriaxone for certain strains may reach 0.015 to 0.125 mg/L [higher than MICs for fully susceptible strains (0.0001 to 0.008 mg/L)], these levels are greatly exceeded in blood, the urethra, and the cervix when the routinely recommended ceftriaxone and cefixime regimens are administered (see below). These regimens almost always result in an effective cure.

Quinolone-containing regimens are also recommended for treatment of gonococcal infections; the fluoroquinolones offer the advantage of antichlamydial activity when administered for 7 days. Serum concentrations following therapeutic dosages of the quinolones exceed theMIC for *N. gonorrhoeae* by ~100-fold. However, quinolone-resistant *N. gonorrhoeae* (QRNG) appeared soon after these agents were first used to treat gonorrhea, particularly in Southeast Asia. QRNG strains have been reported recently in the United States, mostly in the far western states. Alterations in DNA gyrase and topoisomerase IV have been implicated as mechanisms of fluoroquinolone resistance.

Resistance to spectinomycin, which is used as an alternative agent, has been reported, but resistance to this agent is usually not associated with resistance to other antibiotics. Therefore, spectinomycin can be reserved for use against multiresistant strains of *N. gonorrhoeae*. Nevertheless, outbreaks caused by strains resistant to spectinomycin have been documented in Korea and England when the drug was used as a primary agent to treat gonorrhea.

Although clinical isolates of *N. gonorrhoeae* vary in their antimicrobial susceptibility

patterns in different parts of the world, they remain susceptible to a wide variety of agents. Because failure of treatment can lead to continued transmission and the emergence of antibiotic resistance, the importance of adequate treatment with a regimen that the patient will adhere to cannot be overemphasized. Thus highly effective single-dose regimens have been developed for the treatment of uncomplicated gonococcal infections. The 1998CDCtreatment guidelines for gonococcal infections are summarized inTable 147-1; the recommendations for uncomplicated gonorrhea apply to HIV-infected as well as HIV-uninfected patients. The third-generation cephalosporins cefixime and ceftriaxone are the mainstay of therapy for uncomplicated gonococcal infection of the urethra, cervix, rectum, or pharynx. Single doses of ciprofloxacin or ofloxacin are also effective first-line regimens. Because of resistance to fluoroquinolones in several parts of Southeast Asia, these agents can no longer be considered effective in that region. Because co-infection with *C. trachomatis* occurs frequently, initial treatment regimens must incorporate an agent (e.g., azithromycin or doxycycline) effective against chlamydial infection. Pregnant women with gonorrhea should receive concurrent treatment with a macrolide antibiotic for possible *Chlamydia* infection; doxycycline should not be used during pregnancy. A single 1-g dose of azithromycin, which is effective therapy for uncomplicated chlamydial infections, results in an unacceptably low cure rate (93%) for gonococcal infections and should not be used alone. Uncomplicated gonococcal infections in penicillin-allergic persons who cannot tolerate quinolones may be treated with a single dose of spectinomycin. Persons with uncomplicated infections who receive a recommended regimen need not return for a test of cure. Cultures for *N. gonorrhoeae* should be performed if symptoms persist after therapy with an established regimen, and any gonococci isolated should be tested for antimicrobial susceptibility.

Symptomatic gonococcal pharyngitis is more difficult to eradicate than genital infection. Few regimens result in cure rates of >90%. Persons who cannot tolerate cephalosporins or quinolones can be treated with spectinomycin, but this agent results in a cure rate of £52%. Therefore, persons given spectinomycin should have a pharyngeal culture performed 3 to 5 days after treatment as a test of cure.

Treatments for gonococcal epididymitis and PID are discussed in Chaps. 132 and133, respectively. Ocular gonococcal infections in older children and adults should be managed with a single dose of ceftriaxone combined with saline irrigation of the conjunctivae (both undertaken expeditiously), and patients should undergo a careful ophthalmologic evaluation that includes a slit-lamp examination.

DGImay require higher dosages and longer durations of therapy (Table 147-1). Hospitalization is indicated if the diagnosis is uncertain, if the patient has localized joint disease that requires aspiration, or if the patient cannot be relied on to comply with treatment. Open drainage is necessary only occasionally, e.g., for management of hip infections that may be difficult to drain percutaneously. Nonsteroidal anti-inflammatory agents may be indicated to alleviate pain and hasten improvement of affected joints. Gonococcal meningitis and endocarditis should be treated in the hospital with high-dose intravenous ceftriaxone (1 to 2 g every 12 h); therapy should continue for 10 to 14 days for meningitis and for at least 4 weeks for endocarditis. All persons who experience more than one episode of DGI should be evaluated for complement deficiency.

## PREVENTION AND CONTROL

Condoms, if properly used, provide effective protection against the transmission and acquisition of gonorrhea as well as other infections that are transmitted to and from genital mucosal surfaces. Spermicidal preparations used with a diaphragm or cervical sponges impregnated with nonoxynol 9 offer some protection against gonorrhea and chlamydial infection. However, the frequent use of preparations that contain nonoxynol 9 is associated with mucosal disruption that paradoxically may enhance the risk of HIV infection in the event of exposure. All patients should be instructed to refer sex partners for evaluation and treatment. All sex partners of persons with gonorrhea should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections if their last contact with the patient took place within 60 days before the onset of symptoms or the diagnosis of infection in the patient. If the patient's last sexual encounter was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated. Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms. Greater emphasis must be placed on prevention by public health education, individual patient counseling, and behavior modification. Preventing the spread of gonorrhea may help reduce the transmission of HIV. No effective vaccine for gonorrhea is yet available, but efforts to test a porin vaccine candidate are under way.

**ACKNOWLEDGEMENT**

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(Bibliography omitted in Palm version)

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Back to Table of Contents

## 148. *MORAXELLA CATARRHALIS* AND OTHER *MORAXELLA* SPECIES - *Daniel M. Musher*

## *MORAXELLA CATARRHALIS*

The gram-negative coccus now known as *Moraxella catarrhalis* has undergone three changes of name in as many decades. Originally called *Micrococcus catarrhalis*, it was renamed *Neisseria catarrhalis* in the 1960s because of its morphologic similarity to *Neisseria* spp. Then, in 1970, it was elevated to the status of a distinct genus, *Branhamella*, on the basis of DNA homology. In 1979 this organism was placed into the genus *Moraxella*, of which *Branhamella* may be a subgenus. A component of the normal bacterial flora of the upper airways, *M. catarrhalis* has been increasingly recognized as a cause of otitis media, sinusitis, and bronchopulmonary infection.

### BACTERIOLOGY AND IMMUNITY

On Gram's staining, *M. catarrhalis* organisms appear as gram-negative cocci, sometimes occurring in pairs and retaining the side-by-side kidney-bean configuration of *Neisseria* (Plate VI-1). These cocci tend to retain crystal violet during the decolorizing step and may be confused with *Staphylococcus aureus*. *Moraxella* colonies grow well on blood or chocolate agar but may be overlooked because of their resemblance to *Neisseria* spp. (a major component of the normal pharyngeal flora). *Moraxella* is readily distinguishable from *Neisseria* spp. by biochemical tests.

Strains of *M. catarrhalis* show a surprising degree of homogeneity in terms of their outer-membrane proteins. Antibody to some of these proteins is generally present in serum of children over the age of 4 years; however, colonizing or disease-causing isolates may survive in serum despite this naturally present antibody and complement. Bactericidal antibody emerges following natural infection and may be directed against one or more conserved outer-membrane proteins -- a property of potential value in vaccine development. The presence of certain outer-membrane proteins is associated with virulence in mice, and antibody may be protective. These proteins are under investigation for use as vaccines.

### EPIDEMIOLOGY

With repeated cultures and the use of selective media, *M. catarrhalis* can be isolated from the upper respiratory tract or saliva of 50% of healthy schoolchildren and of up to 7% of healthy adults. When conventional microbiologic techniques are used, *Moraxella* can be isolated from sputum of about 10% of persons who have chronic bronchitis and 25% of those who have bronchiectasis in the absence of acute infection. Investigators in both the northern and southern hemispheres have reported a striking seasonal variation in the isolation of this organism from clinical specimens, with a peak in late winter/early spring and a nadir in late summer/early fall. Direct contact has not been shown to contribute to community-acquired infection, but nosocomial spread of infection has been documented occasionally.

### OTITIS MEDIA AND SINUSITIS

*M. catarrhalis* has repeatedly been shown to be the third most common bacterial isolate from middle-ear fluid of children who have otitis media, being surpassed only by *Streptococcus pneumoniae* and nontypable *Haemophilus influenzae*. Recent studies have shown that this organism is also a prominent isolate from sinus cavities in acute and chronic sinusitis.

## PURULENT TRACHEOBRONCHITIS AND PNEUMONIA

*M. catarrhalis* causes acute exacerbations of chronic bronchitis (increased production and/or purulence of sputum), purulent tracheobronchitis (the latter also involving fever and leukocytosis), and pneumonia. The great majority of infected persons are>50 years old and have a long history of cigarette smoking and underlying chronic obstructive pulmonary disease (COPD); many have lung cancer as well. In one study, 76% of affected persons had COPD (severe in many cases), and one-third of those with COPD had lung cancer; most patients also had clinical evidence of malnutrition. In one extensive series of cases, *M. catarrhalis* pneumonia did not occur in otherwise-healthy hosts.

Symptoms of *M. catarrhalis* infection have been regarded as modest in severity. Both cough and the amount and purulence of sputum are usually increased above baseline. Chills are reported in one-quarter of patients, pleuritic pain in one-third, and malaise in 40%. Most patients have peak temperatures of<38.3°C (<101°F), and peripheral white blood cell counts are <10,000/uL in nearly one-quarter of cases. Microscopic examination of a good sputum specimen following Gram's staining regularly reveals profuse organisms, and quantitative culture yields ~ 2 ´ $10^8$ colony-forming units per milliliter (Plate VI-1). The radiologic appearance is variable; in one study, 43% of subjects had segmental or lobar infiltrates, and the remainder had a mixed pattern of subsegmental, segmental, interstitial, and diffuse involvement. These clinical, laboratory, and radiographic findings do not differ from those of pneumococcal or *Haemophilus* pneumonia in an older patient population. However, a far lesser degree of bloodstream invasion occurs in *M. catarrhalis* infection; in one series, none of 25 patients with *M. catarrhalis* pneumonia had bacteremia. Nevertheless, pneumonia due to *M. catarrhalis* is a marker for severe underlying disease: nearly half of patients die within 3 months of onset.

## OTHER SYNDROMES

Local extension causing empyema is very uncommon, and, as might be inferred from the low rate of bacteremia, metastatic complications of *M. catarrhalis* pneumonia, such as septic arthritis, are exceedingly rare. As of 1995, 58 cases of bacteremic infection due to *M. catarrhalis* had been reported, mainly in children<10 years old or adults>60 years old; most of these patients were immunocompromised. The syndromes reported have included bacteremia with no apparent focus, pneumonia, endocarditis, and meningitis. A petechial or purpuric rash, reminiscent of that observed in meningococcal sepsis and associated with disseminated intravascular coagulation, has been described in a few cases.

## TREATMENT

Treatment of *M. catarrhalis* infection with a penicillin/clavulanic acid combination seems highly appropriate. Penicillin resistance first appeared in *Branhamella* isolates in the mid-1970s and is now found in 85% of clinical isolates. Resistance is mediated by two closely relatedb-lactamases, BRO-1 and BRO-2, which are present in 90% and 10% of resistant isolates, respectively. These enzymes are active against penicillin, ampicillin, and amoxicillin but less so against cephalosporins, especially third-generation cephalosporins, and they bind avidly to clavulanic acid and sulbactam.

Cephalosporins, especially those of the second and third generations, are effective alternatives. Isolates in the United States are also nearly uniformly susceptible to tetracycline, erythromycin, trimethoprim-sulfamethoxazole, quinolones, and chloramphenicol, although tetracycline resistance -- perhaps due to TetB determinants -- is increasing in Europe and Asia and has been documented in the United States. A 5-day course of therapy has been shown to cure respiratory infection, although a slightly longer course may be required in sinusitis.

During the period between the identification of gram-negative cocci in a Gram-stained specimen and the final identification of the organisms by culture, the severity of the condition and the potential presence of other infecting organisms should guide antibiotic selection. For example, an exacerbation of bronchitis caused by *M. catarrhalis* might be treated with tetracycline or trimethoprim-sulfamethoxazole; however, in a patient with pneumonia, the possibility that pneumococci resistant to these agents also might be present dictates the choice of ampicillin/sulbactam or a third-generation cephalosporin, at least until culture results become available.

## OTHER *MORAXELLA* SPECIES

Other *Moraxella* species cause a wide range of infections, including bronchitis, pneumonia, empyema, endocarditis, meningitis, conjunctivitis, urinary tract infection, septic arthritis, and wound infection. In a report on all *Moraxella* isolates submitted to the Centers for Disease Control and Prevention between 1953 and 1980, certain clinical associations were apparent (Table 148-1). *M. osloensis* and *M. nonliquefaciens*, the most commonly isolated species, were cultured from a wide range of normally sterile body sites, including blood, cerebrospinal fluid, and joints. *M. osloensis* was the *Moraxella* species most frequently isolated from blood; *M. nonliquefaciens* tended to be isolated from the ears, nose, or throat (47%) or the sputum (8%) and has since been implicated as a cause of conjunctivitis and keratitis. *M. urethralis* was isolated most often from urine and the genital tract and probably represents the *Moraxella* species implicated previously in urethritis. More than half of isolates of *M. phenylpyruvica* and *M. atlantae* were obtained from normally sterile sites. A recent study found *Moraxella* spp., including *M. catarrhalis*, in 35% of infected wounds following cat bites and in 10% of those following dog bites. The clinical features of infections due to *Moraxella* spp. other than *M. catarrhalis* and the nature of the hosts in which they occur have not been fully characterized.

(Bibliography omitted in Palm version)

Back to Table of Contents

# 149. *HAEMOPHILUS* INFECTIONS - *Timothy F. Murphy*

## *HAEMOPHILUS INFLUENZAE*

### MICROBIOLOGY

*Haemophilus influenzae* was first recognized in 1892 by Pfeiffer, who erroneously concluded that the bacterium was the cause of influenza. The bacterium is a small (1- by 0.3-um) gram-negative organism of variable shape; hence, it is often described as a pleomorphic coccobacillus. In clinical specimens such as cerebrospinal fluid (CSF) and sputum, it frequently stains only faintly with phenosafranin and therefore can easily be overlooked.

*H. influenzae* grows both aerobically and anaerobically. Its aerobic growth requires two factors: hemin (X factor) and nicotinamide adenine dinucleotide (V factor). These requirements are used in the clinical laboratory to identify the bacterium. Six major serotypes of *H. influenzae* have been identified; designated *a* through *f*, they are based on antigenically distinct polysaccharide capsules. In addition, some strains lack a polysaccharide capsule and are referred to as *nontypable* strains. Type b and nontypable strains are the most relevant strains clinically, although encapsulated strains other than type b can cause disease. *H. influenzae* was the first free-living organism to have its entire genome sequenced.

The antigenically distinct type b capsule is a linear polymer composed of ribosyl-ribitol phosphate. Strains of *H. influenzae* type b (Hib) cause disease primarily in infants and children under the age of 6 years. Nontypable strains are primarily mucosal pathogens, although the incidence of invasive disease caused by these strains is increasing.

### EPIDEMIOLOGY AND TRANSMISSION

*H. influenzae* is an exclusively human pathogen. The organism is spread by airborne droplets or by direct contact with secretions or fomites. Nontypable strains colonize the upper respiratory tract of up to three-fourths of healthy adults. Colonization with nontypable *H. influenzae* is a dynamic process; new strains are acquired and other strains are replaced periodically.

Hibstrains colonize the nasopharynx of children at a rate of 3 to 5%; before the introduction of type b vaccine, higher rates were seen in day-care centers. The widespread use of conjugate vaccines has resulted in a striking decrease not only in the rate of nasopharyngeal colonization by Hib but also in the incidence of meningitis due to Hib. Studies in selected populations suggest the reemergence of invasive Hib infections and higher than expected rates of nasopharyngeal colonization by Hib in vaccinated children. Continued surveillance of Hib disease and colonization rates will be important in evaluating the success of current vaccination strategies.

Certain population groups have a higher incidence of invasiveHibdisease than the general population. The incidence of meningitis due to Hib has been three to four times higher among black children than among white children in several studies. In some Native American groups, the incidence of invasive Hib disease is 10 times higher than

that in the general population. Although this increased incidence has not yet been accounted for, several factors may be relevant, including age at exposure to the bacterium, socioeconomic conditions, and genetic differences in the ability to mount an immune response.

## PATHOGENESIS

Hibstrains cause systemic disease by invasion and hematogenous spread to distant sites such as the meninges, bones, and joints. The type b polysaccharide capsule is an important virulence factor affecting the bacterium's ability to avoid opsonization and cause systemic disease.

Nontypable strains cause disease by local invasion of mucosal surfaces. Otitis media results when bacteria reach the middle ear by way of the eustachian tube. Adults with chronic bronchitis experience recurrent lower respiratory tract infection due to nontypable strains. The incidence of invasive disease caused by nontypable strains is low but increasing.

## IMMUNE RESPONSE

Antibody to capsule is important in protection from infection byHibstrains. The level of (maternally acquired) serum antibody to the capsular polysaccharide, which is a polymer of polyribitol ribose phosphate (PRP), declines from birth to 6 months of age and, in the absence of vaccination, remains low until around 2 or 3 years of age. The age at the antibody nadir correlates with that of the peak incidence of type b disease. Antibody to PRP then appears partly as a result of exposure to Hib or cross-reacting antigens. Systemic Hib disease is unusual after the age of 6 years because of the presence of protective antibody. Vaccines in which PRP is conjugated to protein carrier molecules have been developed and are now used widely. These vaccines generate an antibody response to PRP in infants and are effective in preventing invasive infections in infants and children.

Since nontypable strains lack a capsule, the immune response to infection is directed at noncapsular antigens. These noncapsular antigens of *H. influenzae* have generated considerable interest as targets of the human immune response and as potential vaccine components.

## CLINICAL MANIFESTATIONS

**Hib** The most serious manifestation of infection withHib is meningitis. The age of peak incidence varies somewhat among populations, depending in part on the use of vaccine, but this infection primarily affects infants under 2 years of age. The clinical manifestations of meningitis caused by Hib are similar to those of meningitis caused by other bacterial pathogens. Fever and altered central nervous system function are the most common features at presentation. Nuchal rigidity may or may not be evident. Subdural effusion, the most common complication, is suspected when, despite 2 or 3 days of appropriate antibiotic therapy, the infant has seizures, hemiparesis, or continued obtundation. The overall mortality from meningitis caused by Hib is approximately 5%, and the rate of morbidity is high. Of survivors, 6% have permanent sensorineural

hearing loss, and about one-fourth have a significant handicap of some type. If more subtle handicaps are sought, up to half of survivors are found to have some neurologic sequelae, such as partial hearing loss and delay in language development.

*Epiglottitis* is a life-threatening infection involving cellulitis of the epiglottis and supraglottic tissues. It can lead to acute upper airway obstruction. Its unique epidemiologic features are its occurrence in an older age group (2 to 7 years old) than otherHibinfections and its absence among Navajo Indians and Alaskan Eskimos. Sore throat and fever rapidly progress to dysphagia, drooling, and airway obstruction.

*Cellulitis* due toHiboccurs in young children. The most common location is on the head or neck, and the involved area sometimes takes on a characteristic bluish-red color. Most patients have bacteremia, and 10% have an additional focus of infection.

Hibcauses *pneumonia* in infants. The infection is clinically indistinguishable from other types of bacterial pneumonia (e.g., pneumococcal pneumonia) except that Hib is more likely to involve the pleura.

Several less common invasive conditions can be important clinical manifestations ofHibinfection in children. These include osteomyelitis, septic arthritis, pericarditis, orbital cellulitis, endophthalmitis, urinary tract infection, abscesses, and bacteremia without an identifiable focus. As has already been mentioned, infections due to Hib are unusual among patients older than 6 years.

**Nontypable *H. influenzae*** Nontypable *H. influenzae* is the second most common cause (after *Streptococcus pneumoniae*) of community-acquired bacterial pneumonia in adults. Nontypable *H. influenzae* pneumonia is especially common among patients with chronic obstructive pulmonary disease (COPD) or AIDS. The clinical features of pneumonia due to *H. influenzae* are similar to those of other types of bacterial pneumonia (including pneumococcal pneumonia). Patients present with fever, cough, and purulent sputum, usually of several days' duration. Chest radiography reveals alveolar infiltrates in a patchy or lobar distribution. Gram-stained sputum contains a predominance of small, pleomorphic, coccobacillary gram-negative bacteria.

Exacerbations ofCOPDcaused by nontypable *H. influenzae* are characterized by increased cough, sputum production, and shortness of breath. Fever is low-grade, and no infiltrates are evident on chest x-ray.

Nontypable *H. influenzae* is one of the three most common causes of childhood otitis media (the other two being *S. pneumoniae* and *Moraxella catarrhalis*). Infants are febrile and irritable, while older children report ear pain. Symptoms of viral upper respiratory infection often precede otitis media. The diagnosis is made by pneumatic otoscopy. An etiologic diagnosis, although not routinely sought, can be established by tympanocentesis and culture of middle-ear fluid.

Nontypable *H. influenzae* also causes puerperal sepsis and is an important cause of neonatal bacteremia. These nontypable strains tend to be of biotype IV and cause invasive disease after colonizing the female genital tract.

Nontypable *H. influenzae* causes sinusitis in adults and children. In addition, the bacterium is a less common cause of various invasive infections that are reported primarily as small-series descriptions and case reports. These infections include empyema, adult epiglottitis, pericarditis, cellulitis, septic arthritis, osteomyelitis, endocarditis, cholecystitis, intraabdominal infections, urinary tract infections, mastoiditis, aortic graft infection, and bacteremia without a detectable focus.

## DIAGNOSIS

The most reliable method for establishing a diagnosis ofHibinfection is recovery of the organism in culture. TheCSF of a patient in whom meningitis is suspected should be subjected to Gram's staining and culture. The presence of gram-negative coccobacilli in Gram-stained CSF is strong evidence for Hib meningitis. Recovery of the organism from CSF confirms the diagnosis. Cultures of other normally sterile body fluids, such as blood, joint fluid, pleural fluid, pericardial fluid, and subdural effusion, are confirmatory in other infections.

Detection ofPRP is an important adjunct to culture in rapid diagnosis. Immunoelectrophoresis, latex agglutination, coagglutination, and enzyme-linked immunosorbent assay are effective in detecting PRP. These assays are particularly helpful when patients have received prior antimicrobial therapy and thus are especially likely to have negative cultures.

Before the early 1980s, nontypable strains of *H. influenzae* were frequently misidentified asHibbecause of their autoagglutination when serotypes were determined in agglutination assays. Since nontypable *H. influenzae* is primarily a mucosal pathogen, it is a component of a mixed flora; this situation makes etiologic diagnosis challenging. Nontypable *H. influenzae* infection is strongly suggested by the predominance of gram-negative coccobacilli among abundant polymorphonuclear leukocytes in a Gram-stained sputum specimen from a patient in whom pneumonia or tracheobronchitis is suspected. A sputum culture is helpful when interpreted along with the results of Gram's staining. Although bacteremia is detectable in a small proportion of patients with pneumonia due to nontypable *H. influenzae*, most such patients have negative blood cultures.

A diagnosis of otitis media is based on the detection by pneumatic otoscopy of fluid in the middle ear. An etiologic diagnosis requires tympanocentesis but is not routinely sought. An invasive procedure is also required to determine the etiology of sinusitis; thus, treatment is often empirical once the diagnosis is suspected in light of clinical symptoms and sinus radiographs.

## TREATMENT

Initial therapy for meningitis due toHibshould consist of a cephalosporin such as ceftriaxone or cefotaxime. For children, the dose of ceftriaxone is 75 to 100 mg/kg daily given in two doses 12 h apart. The pediatric dose of cefotaxime is 200 mg/kg daily given in four doses 6 h apart. Adult doses are 2 g every 12 h for ceftriaxone and 2 g every 4 to 6 h for cefotaxime. An alternative regimen for initial therapy is ampicillin (200 to 300 mg/kg daily in four divided doses) plus chloramphenicol (75 to 100 mg/kg daily in four

divided doses). Therapy should continue for a total of 1 to 2 weeks.

Administration of glucocorticoids to patients withHibmeningitis reduces the incidence of neurologic sequelae. The presumed mechanism is reduction of the inflammation induced by bacterial cell-wall mediators of inflammation when cells are killed by antimicrobial agents. Dexamethasone (0.6 mg/kg per day intravenously in four divided doses for 2 days) is recommended for the treatment of Hib meningitis in children over 2 months of age.

Invasive infections other than meningitis are treated with the same antimicrobial agents. For epiglottitis, the dose of ceftriaxone is 50 mg/kg daily, and the dose of cefotaxime is 150 mg/kg daily, given in three divided doses 8 h apart. Epiglottitis constitutes a medical emergency, and maintenance of an airway is critical. The duration of therapy is determined by the clinical response. A course of 1 to 2 weeks is usually appropriate.

Many infections caused by nontypable strains of *H. influenzae*, such as otitis media, sinusitis, and exacerbations ofCOPD, can be treated with oral antimicrobial agents. Approximately 25% of nontypable strains produce b-lactamase and are resistant to ampicillin. Infections caused by ampicillin-resistant strains can be treated with a variety of agents, including trimethoprim-sulfamethoxazole, amoxicillin/clavulanic acid, various extended-spectrum cephalosporins, and newer macrolides (azithromycin and clarithromycin). Fluoroquinolones are highly active against *H. influenzae* but are not currently recommended for the treatment of children or pregnant women because of possible effects on articular cartilage.

**PREVENTION**

**Vaccination** The development of conjugate vaccines that prevent invasive infections withHib in infants and children has been a dramatic success. Four such vaccines are licensed in the United States. In addition to eliciting protective antibody, these vaccines prevent disease by reducing pharyngeal colonization with Hib.

All children should be immunized with anHibconjugate vaccine, receiving the first dose at approximately 2 months of age, the rest of the primary series between 2 and 6 months of age, and a booster dose at 12 to 15 months of age. Specific recommendations vary for the different conjugate vaccines. The reader is referred to the recommendations of the American Academy of Pediatrics. Currently, no vaccines are available for the prevention of disease caused by nontypable *H. influenzae*.

**Chemoprophylaxis** The risk of secondary disease is greater than normal among household contacts of patients withHibdisease. The attack rate is as high as 4% among susceptible infants. Therefore, all children and adults in households where there are contacts<4 years old should receive prophylaxis with oral rifampin. (This rule does not apply when all household contacts under the age of 4 years have been completely immunized with conjugate vaccine.) Children<12 years old should receive rifampin at a dose of 20 mg/kg once daily for 4 days, and adults should receive 600 mg daily for 4 days. The index case should receive rifampin before or at the time of discharge from the hospital because antimicrobial agents used for the treatment of meningitis do not reliably eradicate Hib from the nasopharynx.

When two or more cases of invasiveHibdisease have occurred within 60 days at a child-care facility attended by incompletely vaccinated children, administration of rifampin to all attendees and personnel is indicated, as is recommended for household contacts. The data on secondary cases among contacts in child-care facilities following a single case are less clear. The administration of rifampin prophylaxis to contacts should be considered, but each decision should be individualized and in part based on the contacts' immunization history, the size of the center, and the extent of contact.

## *HAEMOPHILUS INFLUENZAE* BIOGROUP AEGYPTIUS

*H. influenzae* biogroup aegyptius was formerly called *Haemophilus aegyptius* because of phenotypic characteristics distinct from those of *H. influenzae*. However, later studies involving DNA hybridization and DNA transformation demonstrated that *H. aegyptius* and *H. influenzae* are members of the same species.

*H. influenzae* biogroup aegyptius has long been associated with conjunctivitis. Moreover, this strain is now known to be the cause of Brazilian purpuric fever (BPF), which was first recognized in 1984 in the rural Brazilian town of Promissao. The sharing of many phenotypic and genotypic characteristics by the various strains of *H. influenzae* biogroup aegyptius that cause BPF indicates that these strains represent a clone of *H. influenzae*. The age of peak incidence of BPF is 1 to 4 years, with a range of 3 months to 8 years. The illness can occur sporadically or in outbreaks. Typically, after an episode of purulent conjunctivitis, high fever occurs in association with vomiting and abdominal pain. Within 12 to 48 h after onset, the patient develops petechiae, purpura, and peripheral necrosis and experiences vascular collapse. The characteristic laboratory features are thrombocytopenia, prolonged prothrombin time, uniformly unrevealingCSFfindings, and blood cultures positive for *H. influenzae* biogroup aegyptius. Initial reports cited high mortality (70%), but subsequent studies have indicated that milder forms of the illness exist. Most patients have resolved or resolving purulent conjunctivitis, and culture of the conjunctiva is positive in approximately one-third of cases. BPF has been seen in several towns in Brazil and on two occasions in Australia.

## *HAEMOPHILUS DUCREYI*

*Haemophilus ducreyi* is the etiologic agent of chancroid, a sexually transmitted disease characterized by genital ulceration and inguinal adenitis. *H. ducreyi* poses a significant health problem in developing countries. Although this infection is less common in the United States, its incidence has increased dramatically in the past several years. In addition to being a cause of morbidity in itself, chancroid is associated with infection with HIV because of the role of genital ulceration in the transmission of HIV.

### MICROBIOLOGY

*H. ducreyi* is a highly fastidious coccobacillary gram-negative bacterium whose growth requires X factor (hemin). Although, in light of this requirement, the bacterium has been classified in the genus *Haemophilus*, DNA homology and chemotaxonomic studies have established substantial differences between *H. ducreyi* and other *Haemophilus* species.

Taxonomic reclassification of the organism is likely in the future but awaits further study.

The histology of the genital ulcer of chancroid is characterized by perivascular and interstitial infiltrates of macrophages and of CD4+ and CD8+ lymphocytes. The appearance is consistent with a delayed-type hypersensitivity, cell-mediated immune response. The presence of CD4+ cells and macrophages in the ulcer may explain, in part, the facilitation of transmission of HIV in patients with chancroid.

## EPIDEMIOLOGY AND PREVALENCE (See also Chap. 132)

Chancroid is a common cause of genital ulcers in developing countries. In the United States, chancroid is now endemic in some regions, and several large outbreaks have occurred since 1981. Recurring epidemiologic themes have been apparent in these outbreaks: (1) transmission has been predominantly heterosexual; (2) males have outnumbered females by ratios of 3:1 to 25:1; (3) prostitutes have been important in transmission of the infection; and (4) chancroid has been strongly associated with illicit drug use. The incidence of chancroid in the United States will undoubtedly increase in the coming years, and the genital ulcers associated with this infection will continue to play a role in the transmission of HIV.

## CLINICAL MANIFESTATIONS

Infection is acquired as the result of a break in the epithelium during sexual contact with an infected individual. After an incubation period of 4 to 7 days, the initial lesion -- a papule with surrounding erythema -- appears (Plate IID-54). In 2 to 3 days, the papule evolves into a pustule, which spontaneously ruptures and forms a sharply circumscribed ulcer (Fig. 132-CD1) that is generally not indurated. The ulcers are painful and bleed easily; little or no inflammation of the surrounding skin is evident. Approximately half of patients develop enlarged, tender inguinal lymph nodes, which frequently become fluctuant and spontaneously rupture.

The presentation of chancroid does not usually include all of the typical clinical features and is sometimes atypical. Multiple ulcers can coalesce to form giant ulcers. Ulcers can appear and then resolve, with inguinal adenitis and suppuration following 1 to 3 weeks later; this clinical picture can be confused with that of lymphogranuloma venereum. Multiple small ulcers can resemble folliculitis. Other differential diagnostic considerations include the various infections causing genital ulceration, such as primary syphilis, condyloma latum of secondary syphilis, genital herpes, and donovanosis. In rare cases chancroid lesions become secondarily infected with bacteria; the result is extensive inflammation.

## DIAGNOSIS

Clinical diagnosis of chancroid is often inaccurate, and laboratory confirmation should be attempted in suspected cases. Gram's staining of a swab of the lesion may reveal a predominance of characteristic gram-negative coccobacilli, but the presence of other bacteria often makes it difficult to interpret this result. An accurate diagnosis of chancroid relies on cultures of *H. ducreyi* from the lesion. In addition, aspiration and culture of suppurative lymph nodes should be considered. Since the organism can be

difficult to grow, the use of selective and supplemented media is necessary.

### TREATMENT

Clinical isolates of *H. ducreyi* often exhibit plasmid-mediated resistance to ampicillin, chloramphenicol, tetracyclines, and sulfonamides. Nevertheless, chancroid can be treated effectively with several regimens, including (1) ceftriaxone, 250 mg intramuscularly as a single dose; (2) azithromycin, 1 g orally as a single dose; (3) erythromycin, 500 mg orally four times daily for 7 days; and (4) ciprofloxacin, 500 mg orally twice daily for 3 days. Ciprofloxacin should not be administered to pregnant or lactating women or to persons<18 years old. Any therapeutic regimen may fail; single-dose ceftriaxone has a high failure rate in HIV-positive individuals. Isolates from patients who do not respond promptly to treatment should be tested for antimicrobial susceptibility. In patients with HIV infection, healing may be slow and longer courses of treatment may be necessary. Contacts of patients with chancroid should be identified and treated whenever possible.

## OTHER *HAEMOPHILUS* SPECIES

*Haemophilus* species are often recovered as components of the flora of the normal human upper respiratory tract. However, these bacteria are infrequent causes of infection because of their low pathogenic potential. *Haemophilus* species have fastidious growth requirements and are generally rather slow-growing. The species implicated in human infections include *H. parainfluenzae*, *H. aphrophilus*, and *H. paraphrophilus* (Chap. 150); *H. parahaemolyticus*; *H. haemolyticus*; and *H. segnis*. *Haemophilus* species are differentiated from one another by several characteristics, primarily their requirements for X and V factors. Species designated *para*- require V factor but not X factor for growth, whereas the others require either X and V or X only.

A variety of infections involving almost all organ systems can be caused by *Haemophilus* species. Most of these unusual manifestations have been reported as single cases and small series.

The antimicrobial susceptibility characteristics of other *Haemophilus* species are similar to those of *H. influenzae*. Some strains produce b-lactamase and are thereby resistant to ampicillin. Other strains are sensitive to ampicillin, and this agent has been used successfully to treat many infections. Alternative agents with good activity against most *Haemophilus* species include trimethoprim-sulfamethoxazole, third-generation cephalosporins, tetracycline, chloramphenicol, and aminoglycosides. Endocarditis caused by ampicillin-sensitive strains should be treated with ampicillin plus an aminoglycoside.

(Bibliography omitted in Palm version)

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Back to Table of Contents

# 150. INFECTIONS DUE TO THE HACEK GROUP AND MISCELLANEOUS GRAM-NEGATIVE BACTERIA - *Dennis L. Kasper*, *Tamar F. Barlam*

## HACEK GROUP ORGANISMS

HACEK organisms are a group of fastidious, slow-growing, gram-negative bacteria whose growth requires an atmosphere of carbon dioxide. Species belonging to this group include several ***H***aemophilus species, ***A***ctinobacillus *actinomycetemcomitans*, ***C***ardiobacterium *hominis*, ***E***ikenella *corrodens*, and ***K***ingella *kingae*. HACEK bacteria normally reside in the oral cavity and have been associated with local infections in the mouth. They are also known to cause severe systemic infections, most often bacterial endocarditis (Chap. 126).

Of the HACEK group, the *Haemophilus* species, *A. actinomycetemcomitans*, and *C. hominis* are most frequently associated with endocarditis, which can develop on either native or prosthetic valves. In large series, up to 3% of cases of infective endocarditis are attributable to HACEK organisms. The clinical course of HACEK endocarditis tends to be subacute; however, embolization is common. The overall prevalence of major emboli associated with HACEK endocarditis ranges from 28 to 60% in different series. Cultures of blood from patients with suspected HACEK endocarditis may require up to 30 days to become positive, although most are positive within the first week. Because of this slow growth, antimicrobial testing may be difficult, and strains producingb-lactamase may not be identified accurately. This factor should be considered when choosing a therapeutic regimen.

The cure rates for HACEK prosthetic valve endocarditis appear to be high. Unlike prosthetic valve endocarditis caused by other gram-negative organisms, HACEK endocarditis is often cured with antibiotic treatment alone -- i.e., without surgical intervention.

***Haemophilus* Species** *Haemophilus* species cause over half of all cases of HACEK endocarditis. *H. parainfluenzae* is most common, with *H. aphrophilus* and *H. paraphrophilus* less common. Up to 50% of patients with native valve endocarditis due to *Haemophilus* species report a history of cardiac valvular disease, 60% have been ill for <2 months before presentation, and 50% are anemic at presentation. Some 19% of these patients develop congestive heart failure. Mortality rates of up to 30% have been reported, with most deaths attributed to cerebral embolism; however, recent studies have documented mortality rates of <5%. In rare cases, *H. parainfluenzae* has been isolated from other infections, such as meningitis; brain, dental, and liver abscess; pneumonia; and septicemia.

## TREATMENT

Therapy for endocarditis due to *Haemophilus* species should be based on antibiotic sensitivity testing. Empirical combination therapy with ampicillin and gentamicin, successful in prior studies, is no longer recommended because of increasing b-lactamase production by these strains. Treatment with ceftriaxone (2 g/d) is a reasonable initial approach.

***Actinobacillus actinomycetemcomitans*** *A. actinomycetemcomitans*, another slow-growing inhabitant of the oral cavity, can be isolated from soft tissue infections and abscesses in association with *Actinomyces israelii.* About 30% of actinomycotic lesions also yield *A. actinomycetemcomitans* on culture. *A. actinomycetemcomitans* has been associated with severe destructive periodontal disease, characterized by loss of alveolar bone of the molars and incisors, in both children and adults. Patients who develop endocarditis with this organism typically have severe periodontal disease and underlying cardiac valvular damage as well as high rates of embolic phenomena. *A. actinomycetemcomitans* has been isolated from patients with brain abscess, meningitis, parotitis, osteomyelitis, urinary tract infection, pneumonia, and empyema, among other infections.

**TREATMENT**

Most isolates are susceptible to third-generation cephalosporins such as ceftriaxone (2 g/d), semisynthetic penicillins such as mezlocillin, trimethoprim-sulfamethoxazole, quinolones, and azithromycin. However, because of the variability among strains, susceptibility testing should be undertaken. Endocarditis should normally be treated for 4 weeks; however, prosthetic valve infections or infections in patients with complications such as embolization justify 6 weeks of therapy.

***Cardiobacterium hominis*** *C. hominis* primarily causes endocarditis in patients with underlying valvular heart disease or with prosthetic valves. Many patients have signs and symptoms of long-standing infection before diagnosis and have evidence of arterial embolization, vasculitis, cerebrovascular accidents, immune complex glomerulonephritis, or arthritis at presentation. As in endocarditis due to other HACEK organisms, embolization, mycotic aneurysms, and congestive heart failure are frequent.

**TREATMENT**

Antibiotic sensitivity testing of *C. hominis* is difficult. Most cases of infection due to *C. hominis* are treated with penicillin (16 to 18 million units per day in 6 divided doses), either alone or in combination with an aminoglycoside (e.g., gentamicin, 5 to 6 mg/kg per day in 3 divided doses). The value of the aminoglycoside in this situation has not been established.

***Eikenella corrodens*** *E. corrodens*, a fastidious, facultative gram-negative organism, is part of the endogenous flora of the mouth and nasopharynx. It is most frequently recovered from sites of infection in conjunction with other bacterial species. Clinical sources of *E. corrodens* include sites of human bite wounds (clenched-fist injuries), endocarditis, soft tissue infections of the head and neck, soft tissue infections in injection drug users, osteomyelitis, respiratory infections, chorioamnionitis, gynecologic infections associated with intrauterine devices, meningitis and brain abscesses, and visceral abscesses.

**TREATMENT**

*E. corrodens*-associated infections can be treated with ampicillin (2 g every 4 h) or with second- or third-generation cephalosporins. The organism is susceptible to the

fluoroquinolones in vitro but is resistant to metronidazole and clindamycin.

***Kingella kingae*** *K. kingae* is a b-hemolytic, fastidious, nonmotile gram-negative rod. Because of improved microbiologic methodology, isolation of this organism is increasingly common. In young children, *K. kingae* causes septic arthritis and osteomyelitis. In several series, *K. kingae* has been the third most common cause of septic arthritis in children<24 months of age; staphylococcal and streptococcal species remain most prevalent. In children <4 years of age, there is evidence for prolonged nasopharyngeal colonization, with carriage rates of 10%. Invasive *K. kingae* infections with bacteremia are associated with stomatitis. Both *K. kingae* colonization and primary herpes -- a major cause of stomatitis -- peak in children 6 to 48 months of age. *K. kingae* bacteremia can present with a petechial rash similar to that seen with *Neisseria meningitidis* sepsis.

Infective endocarditis, unlike other infections with *K. kingae*, occurs in older children and adults. The majority of patients have preexisting valvular disease. As in endocarditis caused by the other HACEK organisms, there is a high incidence of complications, including arterial emboli, cerebrovascular accidents, tricuspid insufficiency, and congestive heart failure with cardiovascular collapse.

**TREATMENT**

*K. kingae* can be susceptible to ampicillin, second- and third-generation cephalosporins, fluoroquinolones, vancomycin, clindamycin, macrolides, and trimethoprim-sulfamethoxazole. Because of increasingb-lactamase production in *K. kingae* strains, susceptibility testing should be performed to guide therapy. Ceftriaxone (2 g/d) or ampicillin-sulbactam (3 g of ampicillin every 6 h) are both appropriate choices for initial therapy.

## OTHER GRAM-NEGATIVE BACTERIA

***Acinetobacter*** **Species** See Chap. 153.

***Achromobacter xylosoxidans*** Previously known as *Alcaligenes xylosoxidans*, the gram-negative bacillus *Achromobacter xylosoxidans* is probably part of the endogenous intestinal flora and has been isolated from water sources. Immunocompromised hosts appear to be at increased risk for infection with this organism. Nosocomial sources to which outbreaks of infection with *A. xylosoxidans* have been attributed include contaminated intravenous fluids, pressure transducers, and disinfectants. Clinical illness has been associated with isolates from many sites, including blood (often in the setting of infected intravascular devices), urine, respiratory secretions, cerebrospinal fluid, peritoneal and pleural fluids, and endocarditic prosthetic valves. Community-acquired bacteremia with *A. xylosoxidans* usually occurs in the setting of pneumonia. Metastatic skin lesions are present in one-fifth of cases. The reported mortality rate is 67%, similar to rates for other bacteremic gram-negative pneumonias.

**TREATMENT**

In vitro susceptibility testing of all clinically relevant isolates is essential to the selection

of appropriate therapy.

***Agrobacterium radiobacter (tumefaciens)*** This organism has been associated with intravascular catheter-related infections in immunocompromised hosts, especially individuals infected with HIV. Clinically important infections associated with *A. radiobacter* include prosthetic joint and prosthetic valve infections, bacteremia, peritonitis, and urinary tract infections.

**TREATMENT**

Antibiotic sensitivity testing is essential in the choice of therapy.

***Capnocytophaga* Species** This genus of fusiform, long, thin, gram-negative coccobacilli is facultatively anaerobic and requires an atmosphere enriched in carbon dioxide for optimal growth. *C. ochracea*, *C. gingivalis*, and *C. sputigena* are inhabitants of the healthy human oral cavity and have been isolated from the female genital tract. Their isolation has also been reported from blood, cerebrospinal fluid, and respiratory fluids (including pleural collections). These organisms have been associated with sepsis in immunocompromised hosts; particularly at risk are patients with acute myelogenous leukemia or acute lymphocytic leukemia. In the immunocompetent host, these three species probably play a role in localized juvenile periodontitis; however, they have been isolated from many other sites as well, usually as part of a polymicrobial infection. In vitro sensitivity testing of these organisms is difficult because they are slow-growing and fastidious.

*C. canimorsus* and *C. cynodegmi* are endogenous to the canine mouth. Patients infected with these species frequently have a history of dog bites or of exposure to dogs without scratches or bites. Asplenia, glucocorticoid therapy, and alcohol abuse are predisposing conditions and are associated with relatively fulminant infections. The interval from dog bite to presentation averages 5 days but ranges from 1 day to 1 month. *C. canimorsus* causes a wide range of infections, including severe sepsis with shock and disseminated intravascular coagulation, meningitis, endocarditis, cellulitis, and septic arthritis. In the asplenic individual who has recently sustained a dog bite, infection with this organism must be considered early because of a potentially rapid progression to death.

**TREATMENT**

Although penicillin has been considered first-line therapy for infections due to *C. ochracea*, *C. gingivalis*, and *C. sputigena*, an increasing number of isolates reportedly produce b-lactamase. Clindamycin (600 to 900 mg every 6 to 8 h) or drug combinations including a penicillin derivative plus a b-lactamase inhibitor -- such as ampicillin/sulbactam (1.5 to 3.0 g of ampicillin every 6 h) -- are currently recommended for empirical therapy. Penicillin (12 to 18 million units daily in 6 divided doses) is the drug of choice for infections with *C. canimorsus*. This regimen should also be given prophylactically to asplenic patients sustaining dog-bite injuries. Patients with suspected infection due to *C. canimorsus* should be treated empirically, because identification of this organism and determination of its antibiotic sensitivity can take many days. Other drugs to which *C. canimorsus* is reportedly susceptible include clindamycin, imipenem,

quinolones, and third-generation cephalosporins.

***Chromobacterium violaceum*** This organism is rarely a human pathogen but reportedly has been responsible for life-threatening infections with severe sepsis and metastatic abscesses. A slender, slightly curved, gram-negative rod that is facultatively anaerobic, *C. violaceum* inhabits tropical water and soil and causes infection after contamination of skin wounds. Patients with defective neutrophil function (e.g., those with chronic granulomatous disease) are infected by this organism with unusual frequency. The mortality rate in the United States from infection with *C. violaceum* has been reported at>60%.

**TREATMENT**

*C. violaceum* is generally susceptible to ciprofloxacin (500 mg every 12 h orally or 400 mg every 12 h intravenously), trimethoprim-sulfamethoxazole, gentamicin, and chloramphenicol.

***Chryseobacterium* Species** *C. meningosepticum* and *C. indologenes* were previously classified as *Flavobacterium* species. *C. meningosepticum* is a ubiquitous organism and an important cause of nosocomial infections. It has been associated with outbreaks due to contaminated fluids, such as disinfectants, arterial catheter flush solutions, and aerosolized antibiotics, and with sporadic infections due to indwelling devices, vials, sink traps, feeding tubes, and other fluid-associated apparatus. Patients with nosocomial *C. meningosepticum* infection usually have underlying immunosuppression (e.g., related to malignancy). *C. meningosepticum* has been reported to cause meningitis (primarily in neonates), sepsis, endocarditis, bacteremia, soft tissue infections, and pneumonia. *C. indologenes* has caused bacteremia, sepsis, and pneumonia, typically in immunocompromised patients with indwelling devices.

**TREATMENT**

Antibiotic treatment should be based on susceptibility results because of the high likelihood that *C. meningosepticum* will produceb-lactamase. Early reports suggested that vancomycin might be efficacious, but more recent data refute this conclusion.

***Plesiomonas shigelloides*** This freshwater organism is a cause of acute diarrhea (Chap. 131) and occasionally of serious extraintestinal disease. *P. shigelloides* is transmitted to humans via contaminated water or food. This motile, facultatively anaerobic gram-negative rod most often produces mild diarrhea with mucoid, bloody feces containing leukocytes. Severe extraintestinal infections have been reported, most commonly in immunocompromised hosts, and include bacteremia, cellulitis, neonatal sepsis and meningitis, and septic arthritis.

**TREATMENT**

There is great variability among strains in terms of antibiotic sensitivity patterns, and isolates must be tested before appropriate therapy can be selected.

***Aeromonas* Species** Five species of *Aeromonas* are known to be associated with

disease in humans, but >85% of these infections are caused by *A. hydrophila*, *A. caviae*, and *A. veronii* biovar. *sobria*. *Aeromonas* proliferates in potable and fresh water and in soil. It remains controversial whether *Aeromonas* is a cause of bacterial gastroenteritis. Although many case reports have associated *Aeromonas* with gastroenteritis, no clear outbreaks with a single isolate have been documented, no conclusive animal model exists, and asymptomatic colonization of the intestinal tract with *Aeromonas* occurs frequently. However, rare cases of hemolytic-uremic syndrome occurring after bloody diarrhea have been shown to be secondary to the presence of *Aeromonas*. In addition, identification of an enterotoxin (different from the Shiga-like toxin produced by *Escherichia coli* O157:H7) in these cases supports the hypothesis that *Aeromonas* causes gastroenteritis.

*Aeromonas* causes sepsis and bacteremia in infants with multiple medical problems and in immunocompromised hosts, particularly those with cancer or hepatobiliary disease. *Aeromonas* infection and sepsis can occur in trauma patients with myonecrosis or in burn patients exposed to *Aeromonas* by environmental contamination of their wounds from fresh water or soil sources. Mortality ranges from 25% for sepsis in immunocompromised adults to>90% in patients with myonecrosis. *Aeromonas* can produce skin lesions resembling the ecthyma gangrenosum lesions seen in *Pseudomonas aeruginosa* infection. These lesions are hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration.

*Aeromonas* wound infections can occur in healthy adults who sustain minor trauma with environmental contamination, usually water-related; after severe trauma and crush injuries with sepsis and environmental exposure, usually to soil; and in nosocomial infections related to catheters, surgical incisions, or use of leeches. Other clinical manifestations include meningitis, peritonitis, pneumonia, and ocular infections.

## TREATMENT

Treatment should be guided by antimicrobial susceptibility testing. *Aeromonas* species are generally susceptible to fluoroquinolones (e.g., ciprofloxacin at a dosage of 500 mg every 12 h orally or 400 mg every 12 h intravenously), trimethoprim-sulfamethoxazole at a trimethoprim dosage of 10 mg/kg per day in 3 or 4 divided doses, third-generation cephalosporins, and aminoglycosides. However, resistance is increasing.

**Miscellaneous Organisms** Many other gram-negative rods have been reported to cause occasional infections in hosts who are immunologically unprepared to deal with relatively avirulent organisms or who are unfortunate enough to encounter an exceptionally large inoculum. Such organisms include *Weeksella* species; various CDC groups, such as EF-4, Ve-2 (*Flavimonas* species), IVc-2, NO-1, WO-1, and Gilardi Group WO-1; *Sphingobacterium* species; *Protomonas* species; *Ochrobactrum anthropi*; *Oligella urethralis*; and *Shewanella putrefaciens*. The reader is advised to consult subspecialty texts and references for further guidance on these organisms.

(Bibliography omitted in Palm version)

Back to Table of Contents

## 151. *LEGIONELLA* INFECTION - *Feng-Yee Chang*, *Victor L. Yu*

### DEFINITION

*Legionellosis* refers to the two clinical syndromes caused by bacteria of the genus *Legionella*. *Pontiac fever* is an acute, febrile, self-limited illness that has been serologically linked to *Legionella* species, whereas *Legionnaires' disease* is the designation for pneumonia caused by these species.

### HISTORY

Legionnaires' disease was first recognized in 1976, when an outbreak of pneumonia took place at a hotel in Philadelphia during the American Legion Convention. Investigators from the Centers for Disease Control and Prevention (CDC) identified the causative aerobic gram-negative bacterium in lung specimens obtained from the victims at autopsy and named this organism *L. pneumophila*. Retrospective studies of stored serum samples revealed that an epidemic of Legionnaires' disease had occurred in 1957 in Austin, Minnesota. In this epidemic 78 persons were hospitalized with acute respiratory infection. Antibody determinations showed seroconversion to *L. pneumophila* in most cases.

### MICROBIOLOGY

At present, the family Legionellaceae comprises 41 species with 64 serogroups. The species *L. pneumophila* causes 80 to 90% of human infections and includes at least 14 serogroups; serogroups 1, 4, and 6 are most commonly implicated in human infections. To date, 17 species other than *L. pneumophila* have been associated with human infections, among which *L. micdadei* (Pittsburgh pneumonia agent), *L. bozemanii*, *L. dumoffii*, and *L. longbeachae* are the most common.

Members of the Legionellaceae are aerobic, thin, gram-negative bacilli that do not grow on routine microbiologic media. Buffered charcoal yeast extract (BCYE) agar is the medium used to grow *Legionella*. This highly enhanced medium contains the amino acid L-cysteine, which is an absolute growth requirement for *Legionella*. Growth of the organism on BCYE medium is usually visible in 3 to 5 days at 35 to 37°C. *L. micdadei* and *L. maceachernii* produce blue colonies on BCYE medium containing bromocresol purple and bromothymol blue dyes, while the other species produce green colonies.

Antimicrobial agents, including polymyxin B, cefamandole, and vancomycin, are used in *Legionella*-selective media to suppress competing components of the microflora. Although *L. pneumophila* is relatively tolerant to these antibiotics, the drugs may inhibit the growth of other legionellae; for example, cefamandole-containing media suppress the growth of *L. micdadei*.

Traditional biochemical tests are not particularly helpful in distinguishing one *Legionella* species from another. Fatty-acid profile determination by gas-liquid chromatography and ubiquinone analysis allow identification to the genus level. The direct fluorescent antibody (DFA) test can definitively identify a number of individual species. In *L. pneumophila*, lipopolysaccharide is a prominent constituent of the outer membrane, and

the serogroup-specific antigen and antibodies detected by immunofluorescence are directed primarily at the lipopolysaccharide. Both polyclonal and monoclonal DFA reagents are commercially available. The monoclonal antibody reagent is less cross-reactive but is specific for *L. pneumophila*. Genetic analysis has been considered the definitive arbiter for the identification of individual species, with the degree of DNA sequence homology the most common criterion employed. A nucleic-acid hybridization probe reactive to *Legionella* ribosomal RNA, used with a single reagent, can identify a member of the genus within hours.

## ECOLOGY AND TRANSMISSION

The natural habitats for *L. pneumophila* are aquatic bodies, including lakes and streams; *L. longbeachae* has been isolated from soil. Legionellae can survive under a wide range of environmental conditions; for example, the organisms can live for years in refrigerated water samples. Natural bodies of water contain only small numbers of legionellae. However, once the organisms enter human-constructed aquatic reservoirs (such as cooling towers or water-distribution systems), they can grow and proliferate. Factors known to enhance colonization by and amplification of legionellae include warm temperatures (25° to 42°C), stagnation, and scale and sediment. The presence of symbiotic microorganisms, including algae, amebas, ciliated protozoa, and other water-dwelling bacteria, likewise promotes growth of *L. pneumophila*.

Hot-water tanks colonized with *L. pneumophila* are significantly more likely than uncolonized tanks to be cooler (<60°C), to have a vertical configuration, to be older, and to have higher concentrations of calcium and magnesium. Vertical tanks, especially those that are electric coil-heated rather than gas-heated, have a pronounced temperature stratification and thick sediment accumulation at the bottom. Studies have shown that neither a high degree of outward cleanliness nor routine application of maintenance measures decreases the frequency or intensity of *Legionella* colonization. Thus, engineering guidelines and building codes, although often advocated as preventive measures, have relatively little impact on *Legionella* colonization.

The source of *Legionella* is water, but the mode of transmission from the environmental reservoir to the patient remains controversial. Early investigations that implicated cooling towers antedated the discovery that the organism could also exist in potable water distribution systems. It is now known that, in many outbreaks, cases of Legionnaires' disease continued to occur despite disinfection of cooling towers and the potable water supply was the actual source. Koch's postulates have been fulfilled in epidemiologic studies using molecular fingerprinting methods to link potable water sources (rather than cooling towers) to *Legionella* infection in humans. Community-acquired Legionnaires' disease has been linked to colonization of residential and industrial water supplies.

Multiple modes of transmission of *Legionella* to humans exist, including aerosolization, aspiration, and direct instillation into the lung during respiratory tract manipulations. Aspiration may be the predominant mode of transmission, but it is unclear whether *Legionella* enters the lung via oropharyngeal colonization or directly via the drinking of contaminated water. Nasogastric tubes have been linked to nosocomial Legionnaires' disease in several reports; microaspiration of contaminated water was the hypothesized

mode of transmission. Surgery with general anesthesia is a known risk factor that is consistent with aspiration. Especially compelling is the reported 30% incidence of postoperative *Legionella* pneumonia among patients undergoing head and neck surgery in a hospital with a contaminated water supply; aspiration is a recognized sequela in such cases. Studies of patients with hospital-acquired Legionnaires' disease showed that these individuals underwent endotracheal intubation significantly more often and for a significantly longer duration than patients with nosocomial pneumonia of other etiologies.

Aerosolization of legionellae by devices filled with tap water, including nebulizers and humidifiers, has caused cases of Legionnaires' disease. An ultrasonic mist machine in the produce section of a grocery store was implicated in a community outbreak. Pontiac fever has been linked to *Legionella*-containing aerosols from water-using machinery, a cooling tower, air-conditioners, and whirlpools.

## EPIDEMIOLOGY

The incidence of Legionnaires' disease depends on the degree of contamination of the aquatic reservoir, the susceptibility and immune status of the persons exposed to the water from that reservoir, the intensity of exposure, and the availability of specialized laboratory tests on which the correct diagnosis can be based.

Numerous prospective studies have found *Legionella* to rank among the top four microbial causes of community-acquired pneumonia (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Chlamydia pneumoniae* usually ranking first, second, and third), accounting for 3 to 15% of cases. On the basis of a multihospital study of community-acquired pneumonia in Ohio, theCDC has estimated that only 3% of sporadic cases of Legionnaires' disease are correctly diagnosed. Legionellae are responsible for 10 to 50% of nosocomial pneumonias when a hospital's water system is colonized with the organisms. One situation in which the diagnosis of Legionnaires' disease should be considered is that in which the presenting patient has been hospitalized within 10 days before the onset of symptoms. In one study, a number of patients had been discharged from the hospital and readmitted with Legionnaires' disease; molecular fingerprinting showed that the isolates obtained from patients and the isolate from the hospital's water supply were similar.

The most common risk factors for Legionnaires' disease are cigarette smoking, chronic lung disease, advanced age, and immunosuppression. The disease most often develops in elderly men; this predilection is probably related to cigarette smoking. Surgery is a prominent predisposing factor in nosocomial infection, with transplant recipients at highest risk. Nosocomial cases are now being recognized among neonates and among children with immunosuppression or underlying pulmonary disease.

Pontiac fever occurs in epidemics. The high attack rate (>90%) reflects airborne transmission.

## PATHOGENESIS

Legionellae enter the lungs through aspiration or direct inhalation. The organisms

possess pili that may mediate adherence to respiratory tract epithelial cells. Thus, conditions that impair mucociliary clearance, including cigarette smoking, lung disease, or alcoholism, predispose to Legionnaires' disease.

Cell-mediated immunity is the primary mechanism of host defense against *Legionella*, as it is against other intracellular pathogens, including *Mycobacterium tuberculosis*, *Listeria*, and *Toxoplasma*. Alveolar macrophages readily phagocytose legionellae. The attachment of the bacteria to phagocytes is mediated via complement receptors, which attach to the bacterial major outer-membrane protein. Binding to these receptors promotes phagocytosis but fails to trigger an oxidative burst. Although many legionellae are killed, some proliferate intracellularly until the cells rupture; the bacteria are then phagocytosed again by newly recruited phagocytes, and the cycle begins anew. Legionnaires' disease is more common and the disease manifestations are more severe in patients with depressed cell-mediated immunity, including transplant recipients, patients infected with HIV, and patients receiving glucocorticoids. The disease also occurs with unusual frequency among patients with hairy cell leukemia (which is characterized by monocyte deficiency and dysfunction) but not among patients with other types of leukemia.

The role of neutrophils in immunity appears to be minimal: neutropenic patients are not predisposed to Legionnaires' disease. Although *L. pneumophila* is susceptible to oxygen-dependent microbiologic systems in vitro, it resists killing by neutrophils.

The humoral immune system is active against *Legionella*. Type-specific IgM and IgG antibodies are measurable within weeks of infection. In vitro, antibodies promote killing of legionellae by phagocytes (neutrophils, monocytes, and alveolar macrophages). However, antibodies neither enhance lysis by complement nor inhibit intracellular multiplication within phagocytes. Immunized animals develop a specific antibody response, with subsequent resistance to *Legionella* challenge.

Some *L. pneumophila* strains are clearly more virulent than others, although the precise factors mediating virulence remain uncertain. For example, although multiple strains may colonize water-distribution systems, only a few cause disease in patients exposed to that water. At least one surface epitope of *L. pneumophila* serogroup 1 is associated with virulence. *L. pneumophila* serogroup 6 is more commonly involved in nosocomial Legionnaires' disease and is more likely to be associated with a poor outcome.

## PATHOLOGY

The consistent pathologic features of Legionnaires' disease are confined to the lungs. Findings in infected lung tissue range from multifocal pneumonia with patchy lobular inflammation to extensive multilobar consolidation. Visible abscesses with central necrosis were seen in 20% of autopsied cases in one study. On histologic examination, fibrinopurulent pneumonia with intensive alveolitis and bronchiolitis is evident. Lesions of longer standing can have a nodular appearance with a central area of necrosis surrounded by macrophages and other cells. The alveoli are filled with fibrin, neutrophils, and alveolar macrophages.

Usual tissue stains, including Gram's, hematoxylin and eosin, Brown-Brenn, and

methenamine silver, do not reveal the organism. Giminez stain can be used for imprints on fresh or fixed tissue. Dieterle's silver stain or modified Giminez stain, although nonspecific and relatively insensitive, can be used for paraffin-fixed specimens. TheDFAstain is not only specific but also the most sensitive option for visualization of the organism in tissues. Polyvalent DFA stains but not monoclonal DFA stain can be used for formalinized specimens (Fig. 151-CD1). Because the DFA stains are species and serogroup specific, false-negative results can be obtained if the incorrect reagent is used. Thus, culture is the preferred method for diagnosis based on clinical specimens.

## CLINICAL AND LABORATORY FEATURES

**Pontiac Fever** Pontiac fever is an acute, self-limiting, flulike illness with a 24- to 48-h incubation period. Pneumonia does not develop in Pontiac fever. Malaise, fatigue, and myalgias are the most frequent symptoms, occurring in 97% of cases. Fever (usually with chills) develops in 80 to 90% of cases and headache in 80%. Other symptoms (seen in fewer than 50% of cases) include arthralgias, nausea, cough, abdominal pain, and diarrhea. Modest leukocytosis with a neutrophilic predominance is sometimes detected. Complete recovery takes place within only a few days without antibiotic therapy; a few patients may experience lassitude for many weeks thereafter. The diagnosis is established by antibody seroconversion.

**Legionnaires' Disease (Pneumonia)** Clinical findings that raise the possibility of Legionnaires' disease are summarized in Table 151-1. Although these manifestations may provide clues to the diagnosis, prospective comparative studies have shown that they are generally nonspecific and do not serve to distinguish Legionnaires' disease from pneumonia of other etiologies. Legionnaires' disease is often included in the differential diagnosis of "atypical pneumonia," along with infection due to *Chlamydia pneumoniae*, *C. psittaci*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, and some viruses. The clinical similarities among these types of pneumonia include a relatively nonproductive cough and a low incidence of grossly purulent sputum. However, the clinical manifestations of Legionnaires' disease are usually more severe than those of most "atypical" pneumonias, and the course and prognosis of *Legionella* pneumonia more resemble those of bacteremic pneumococcal pneumonia than those of pneumonia due to other "atypical" pathogens. Patients with community-acquired Legionnaires' disease are significantly more likely than patients with pneumonia of other etiologies to be admitted to an intensive care unit on presentation.

The incubation period for Legionnaires' disease is 2 to 10 days. The symptoms and signs may range from a mild cough and a slight fever to stupor with widespread pulmonary infiltrates and multisystem failure. Nonspecific symptoms -- malaise, fatigue, anorexia, and headache -- are seen early in the illness. Myalgias and arthralgias are uncommon but are unusually marked in a few patients. Upper respiratory symptoms, including coryza, are rare.

The mild cough of Legionnaires' disease is only slightly productive. Sometimes the sputum is streaked with blood. Chest pain -- either pleuritic or nonpleuritic -- can be a prominent feature and, when coupled with hemoptysis, can lead to an incorrect diagnosis of pulmonary embolism. Shortness of breath is reported by one-third to one-half of patients.

Gastrointestinal difficulties are often pronounced; abdominal pain, nausea, and vomiting affect 10 to 20% of patients. Diarrhea (watery rather than bloody) is reported in 25 to 50% of cases. The most common neurologic abnormalities are confusion or changes in mental status; however, the multitudinous neurologic symptoms reported range from headache and lethargy to encephalopathy.

Patients with Legionnaires' disease virtually always have fever. Temperatures in excess of 40.5°C (104.9°F) were recorded in 20% of the cases in one series. Relative bradycardia has been overemphasized as a useful diagnostic finding; it occurs infrequently, primarily affecting older patients with severe pneumonia. Chest examination reveals rales early in the course and evidence of consolidations as the disease progresses. Abdominal examination may reveal generalized or local tenderness.

Diarrhea and hyponatremia occur significantly more often in Legionnaires' disease than in other forms of pneumonia. Hyponatremia is most common in severe cases. The mechanism of hyponatremia does not appear to be related to inappropriate secretion of antidiuretic hormone but instead to salt and water loss. Besides hyponatremia, other laboratory abnormalities include abnormal liver function tests, hypophosphatemia, hematuria, hematologic abnormalities, and thrombocytopenia; although common, these abnormalities are not found significantly more frequently in Legionnaires' disease than in pneumonias of other etiologies.

**Extrapulmonary Legionellosis** Since the portal of entry for legionellae is the lung in virtually all cases, extrapulmonary manifestations usually result from bloodborne dissemination from the lung. In a prospective survey of patients with Legionnaires' disease diagnosed by isolation of the organism from sputum, legionellae were isolated from the blood by a special culture method in 38% of cases.

*Legionella* has been identified in the spleen, liver, or kidneys in 50% of autopsied cases of Legionnaires' disease. The organism has also been isolated from intrathoracic and inguinal lymph nodes -- a finding suggesting dissemination by lymphatic pathways. Extrapulmonary involvement, including sinusitis, peritonitis, pyelonephritis, cellulitis, and pancreatitis, has been documented predominantly in immunosuppressed patients.

The most common extrapulmonary site of legionellosis is the heart; numerous reports have described myocarditis, pericarditis, postcardiotomy syndrome, and prosthetic-valve endocarditis. Most cases have been hospital-acquired. Since many of the patients involved have not had overt pneumonia, the lung may not have been the portal of entry. Rather, in these cardiac infections, the organisms may have gained entry through a postoperative sternal wound exposed to contaminated tap water or through a mediastinal-tube insertion site.

Various other sources of or factors promoting *Legionella* infection at various extrapulmonary sites have been postulated, including the presence of foreign bodies, such as sutures and draining tubes (wound infection after cardiothoracic surgery); immersion in a Hubbard tank (superinfection of a hip wound); bloodborne dissemination from a pulmonary infection site (perirectal abscess); and ingestion of contaminated

water (peritonitis).

**Chest Radiographic Abnormalities** Virtually all patients with Legionnaires' disease have abnormal chest radiographs showing pulmonary infiltrates at the time of clinical presentation. In a few cases of nosocomial disease, fever and respiratory tract symptoms have preceded the appearance of the infiltrate on chest radiography. Findings on chest radiography are nonspecific and do not serve to distinguish Legionnaires' disease from pneumonias of other etiologies. Pleural effusion is evident in one-third of cases, and the diagnosis is often based on culture and antigen testing (by the method designed for use with urine) of pleural fluid obtained by thoracentesis.

In immunosuppressed patients, especially those receiving glucocorticoids, distinctive rounded nodular opacities may be seen; these lesions may expand and cavitate (Fig. 151-1). Likewise, pulmonary abscesses can occur in immunosuppressed hosts. The progression of infiltrates on chest radiography despite appropriate antibiotic therapy is common, and radiographic improvement lags behind clinical improvement by several days. Complete clearing of infiltrates requires 1 to 4 months.

## DIAGNOSIS

The diagnosis of Legionnaires' disease requires special microbiologic tests (Table 151-2). The sensitivity of bronchoscopy specimens is approximately the same as that of sputum samples; if sputum is not available, bronchoscopy specimens may yield the organism. Bronchoalveolar lavage fluid gives higher yields than bronchial wash specimens. Thoracentesis should be performed if pleural effusion is found, and the fluid should be evaluated byDFAstaining, culture, and the antigen test designed for use with urine.

**Staining** Gram's staining of material from normally sterile sites, such as pleural fluid or lung tissue, occasionally suggests the diagnosis; efforts to detect legionellae in sputum by Gram's staining typically reveal numerous leukocytes, but no organisms. When they are visualized, the organisms appear as small, pleomorphic, faint, gram-negative bacilli. *L. micdadei* organisms can be detected as weakly or partially acid-fast bacilli in clinical specimens. Modified acid-fast staining substitutes 1% sulfuric acid for the traditional 3% hydrochloric acid; the less aggressive decolorizer increases the yield of *L. micdadei*. *Legionella*-infected patients have often been treated empirically with antituberculosis medications because of false-positive acid-fast smears.

The DFA test is rapid and highly specific but is less sensitive than culture because large numbers of organisms are required for microscopic visualization. This test is more likely to be positive in advanced than in early disease.

**Culture** The definitive method for diagnosis of *Legionella* infection is isolation of the organism from respiratory secretions or other specimens. As has been mentioned,BCYEagar supplemented with antibiotics and dyes is the most sensitive medium, and colonies grow slowly, requiring 3 to 5 days to become grossly visible. When culture plates are overgrown with other microflora, pretreatment of the specimen with acid or heat can markedly improve the yield. *L. pneumophila* is often isolated from sputum that is not grossly or microscopically purulent; sputum containing more than 25

epithelial cells per high-power field (a finding that classically suggests contamination) may still yield *L. pneumophila*.

**Antibody Detection** Antibody testing of both acute- and convalescent-phase sera may be necessary. A fourfold rise in titer is diagnostic; 4 to 12 weeks are often required for the detection of an antibody response, and some patients never seroconvert. A single titer of 1:128 in a patient with pneumonia constitutes presumptive (but not definitive) evidence for Legionnaires' disease. Serology is of use primarily in epidemiologic studies. The specificity of serology for the non-*L. pneumophila* species is uncertain; there is cross-reactivity with *L. pneumophila* and some gram-negative bacilli.

**Urinary Antigen** The assay for *Legionella* soluble antigen in urine (Binax, Portland, ME) is rapid, relative inexpensive, easy to perform, second only to culture in terms of sensitivity, and highly specific. Its use in every clinical laboratory is recommended. The test is available only for *L. pneumophila* serogroup 1, which, as has been mentioned, causes about 80% of *Legionella* infections. Antigen in urine is detectable 3 days after the onset of clinical disease, even if specific therapy has been started; furthermore, urinary antigen persists for several weeks.

**Molecular Methods** Polymerase chain reaction (PCR) with DNA probes is theoretically more sensitive and specific than other methods, but results have been disappointing to date. PCR has proved useful in the identification of legionellae from environmental water specimens.

## TREATMENT

Controlled evaluations of antibiotic therapy for Legionnaires' disease have never been conducted. In the 1976 American Legion outbreak, patients treated with erythromycin and tetracycline appeared to have a better outcome than those treated with other agents. These two antibiotics also exhibited intracellular activity against legionellae and were effective in animal models. The fact that *Legionella* is an intracellular pathogen provided the biologic basis for the success of erythromycin and tetracycline, given that relatively high intracellular penetration. Antibiotics capable of achieving intracellular concentrations higher than the minimal inhibitory concentration are the most likely to be efficacious in the clinical setting. The dosages for various drugs used in the treatment of *Legionella* infection are listed inTable 151-3.

The newer macrolides (especially azithromycin) and quinolones are now the antibiotics of choice, displacing erythromycin. Compared with erythromycin, the newer agents azithromycin, clarithromycin, and roxithromycin have superior in vitro activity, display greater intracellular activity, and reach higher concentrations in respiratory secretions and in lung tissue. The pharmacokinetics of the newer macrolides and quinolones also allow once- or twice-daily dosing, in contrast to the four-times-daily dosing required for erythromycin. Finally, the large fluid volume required for intravenous administration, symptomatic ototoxicity, and gastrointestinal side effects have rendered erythromycin obsolete for the treatment of *Legionella* infection.

The quinolones (levofloxacin, ciprofloxacin, pefloxacin, gemifloxacin, and moxifloxacin) are more active than any of the macrolides against *Legionella* in in vitro dilution

susceptibility tests, intracellular models, and animal models. Furthermore, in open noncomparative studies of pneumonia, numerous cases of Legionnaires' disease have been successfully treated with quinolones. Quinolones are the preferred antibiotics for transplant recipients because both macrolides (except azithromycin) and rifampin interact pharmacologically with cyclosporine and tacrolimus.

Alternative agents include tetracycline and its analogues doxycycline and minocycline. Anecdotal reports have described both successes and failures with trimethoprim-sulfamethoxazole, imipenem, and clindamycin. For severely ill patients with Legionnaires' disease, the combination of rifampin plus a macrolide or a quinolone can be used for initial treatment.

Initial therapy should be given by the intravenous route. Usually, a clinical response occurs within 3 to 5 days, after which oral therapy can be substituted. The total duration of therapy in the immunocompetent host is 10 to 14 days; a longer course (3 weeks) may be appropriate for immunosuppressed patients and those with advanced disease. In the oral phase, 5 to 10 days of azithromycin is therapy sufficient.

Mortality rates for Legionnaires' disease vary, depending on the patient's underlying disease and its severity, the patient's immune status, the severity of pneumonia, and the timing of administration of appropriate antimicrobial therapy. Mortality rates are highest (80%) among immunosuppressed patients who do not receive appropriate antimicrobial therapy. With appropriate and timely antibiotic treatment, mortality from community-acquired Legionnaires' disease among immunocompetent patients ranges from 0 to 11%; without treatment, the figure may be as high as 31%. Pontiac fever requires only symptom-based treatment, not antimicrobial therapy.

**PREVENTION**

Routine environmental culture of the hospital water supply is recommended as an approach to the prevention of hospital-acquired Legionnaires' disease. Positive cultures from the water supply mandate the use of specialized laboratory tests (especially culture on selective media and urinary antigen assay) for patients with hospital-acquired pneumonia.

Disinfection of the water supply is now feasible. Two methods have proven reliable and cost-effective. The superheat and flush method requires heating of the water so that the distal-outlet temperature is 70 to 80°C and flushing of the distal outlets with hot water for at least 30 min. This method is ideal for emergency situations. A commercial copper and silver ionization method has proved effective in numerous hospitals. Hyperchlorination is no longer recommended because of its expense, carcinogenicity, corrosive effects on piping, and unreliable efficacy.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 152. PERTUSSIS AND OTHER *BORDETELLA* INFECTIONS - *Scott A. Halperin*

Pertussis is an acute infection of the respiratory tract caused by *Bordetella pertussis*. The name *pertussis* means "violent cough," which aptly describes the most consistent and prominent feature of the illness. The inspiratory sound made at the end of an episode of paroxysmal coughing gives rise to the common name for the illness, "whooping cough"; however, this feature is variable, being uncommon in infants £6 months of age and frequently absent in older children and adults. The Chinese name for pertussis is "the 100-day cough," which accurately describes the clinical course of the illness. The identification of *B. pertussis* was first reported by Bordet and Gengou in 1906, and vaccines were produced over the following two decades.

### MICROBIOLOGY

Six species have been identified in the genus *Bordetella*: *B. pertussis*. *B. parapertussis*, *B. bronchiseptica*, *B. avium*, *B. holmesii*, and *B. hinzii*. *B. pertussis* infects only humans and is the most important *Bordetella* species causing human disease. *B. parapertussis* causes an illness in humans that is similar to pertussis but is typically milder; co-infections with *B. parapertussis* and *B. pertussis* have been documented. *B. bronchiseptica* is an important pathogen of domestic animals that causes kennel cough in dogs, atrophic rhinitis and pneumonia in pigs, and pneumonia in cats. Both respiratory infection and opportunistic infection are occasionally reported in humans. *B. avium* is an important cause of respiratory illness in turkeys. The remaining two species, *B. hinzii* and *B. holmesii*, have been recognized as unusual causes of bacteremia. Both of these species have been isolated from patients with sepsis, most often from those who are immunocompromised.

*Bordetella* species are gram-negative pleomorphic aerobic bacilli that share common genotypic characteristics. *B. pertussis* and *B. parapertussis* are the most similar of the species but differ in that *B. parapertussis* does not express the gene coding for pertussis toxin. *B. pertussis* is a slow-growing fastidious organism that requires selective medium and forms small glistening bifurcated colonies. Suspicious colonies are presumptively identified as *B. pertussis* by direct fluorescent antibody testing or by agglutination with species-specific antiserum. *B. pertussis* is further differentiated from other *Bordetella* species by biochemical and motility characteristics.

*B. pertussis* produces a wide array of toxins and biologically active products that are important in its pathogenesis and in immunity. Most of these virulence factors are under the control of a single genetic locus that regulates their production, resulting in antigenic modulation and phase variation. Although these processes occur both in vitro and in vivo, their importance in the pathobiology of the organism is unknown; they may play a role in intracellular persistence and person-to-person spread. The organism's most important virulence factor is *pertussis toxin*, which is composed of a B oligomer-binding subunit and an enzymatically active A protomer that ADP-ribosylates a guanine nucleotide-binding regulatory protein (G protein) in target cells, producing a variety of biologic effects. Pertussis toxin has important mitogenic activity, affects the circulation of lymphocytes, and serves as an adhesin for bacterial binding to respiratory ciliated cells. In animal models, the toxin's effects include histamine sensitization, lymphocytosis promotion, and insulin secretion. Another virulence factor is *filamentous hemagglutinin*,

a component of the cell wall and a bacterial adhesin. *Pertactin* is an outer-membrane protein and another important adhesin. *Fimbriae* are bacterial appendages that also play a role in bacterial attachment; they are the major antigens against which agglutinating antibodies are directed. These agglutinating antibodies have historically been the primary means of serotyping *B. pertussis* strains. Other virulence factors include tracheal cytotoxin, which causes respiratory epithelial damage; adenylate cyclase toxin, which impairs host immune cell function; dermonecrotic toxin, which may contribute to respiratory mucosal damage; and lipo-oligosaccharide, which has properties similar to those of other gram-negative bacterial endotoxins.

## PATHOGENESIS

Infection with *B. pertussis* is initiated by attachment of the organism to the ciliated epithelial cells of the nasopharynx. Attachment is mediated by surface adhesins (e.g., pertactin and filamentous hemagglutinin), which bind to the integrin family of cell-surface proteins, probably in conjunction with pertussis toxin. The role of fimbriae in adhesion or maintenance of infection has not been fully delineated. At the site of attachment, the organism multiplies, producing a variety of other toxins that cause local mucosal damage (tracheal cytotoxin, dermatonecrotic toxin). Impairment of host defense by *B. pertussis* is mediated by pertussis toxin and adenylate cyclase toxin. There is local cellular invasion, with intracellular bacterial persistence; however, systemic dissemination does not occur. Systemic manifestations (lymphocytosis) result from the effects of the toxins.

The pathogenesis of the clinical manifestations of pertussis is poorly understood. It is not known what causes the paroxysmal cough that is the hallmark of pertussis. A pivotal role for pertussis toxin has been proposed. Proponents of this position point to the efficacy of preventing clinical symptoms with a vaccine containing only pertussis toxoid. Detractors counter that pertussis toxin is not the critical factor because paroxysmal cough also occurs in patients infected with *B. parapertussis*, which does not produce pertussis toxin. It is thought that the neurologic events observed in pertussis, such as seizures and encephalopathy, are due to hypoxia from coughing paroxysms or apnea rather than to the effects of specific bacterial products. *B. pertussis* pneumonia, which occurs in up to 10% of infants with pertussis, is usually a diffuse bilateral primary infection. In older children and adults with pertussis, pneumonia is often due to secondary bacterial infection with streptococci or staphylococci.

## IMMUNITY

Both humoral and cell-mediated immunity are thought to be important in pertussis. Antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae are all protective in animal models. Pertussis agglutinins were correlated with protection in early studies of whole-cell pertussis vaccines. Serologic correlates of protection conferred by acellular pertussis vaccines have not been established, although antibody to pertactin, fimbriae, and (to a lesser degree) pertussis toxin correlated best with protection in two acellular pertussis vaccine efficacy trials. The duration of immunity after whole-cell pertussis vaccination is short-lived, with little protection remaining after 10 to 12 years. Data on the duration of protection after acellular pertussis vaccination are still being collected. Although immunity after natural infection has been said to be

lifelong, seroepidemiologic evidence suggests that it may not be and that subsequent episodes of clinical pertussis are prevented by intermittent subclinical infection.

## EPIDEMIOLOGY

Pertussis is a highly communicable disease, with attack rates of 80 to 100% among unimmunized household contacts and 20% within households in well-immunized populations. The infection has a worldwide distribution, with cyclical outbreaks every 3 to 5 years (a pattern that has persisted despite widespread immunization). Pertussis occurs in all months; however, in North America, pertussis activity peaks in the summer and autumn.

Before the institution of widespread immunization programs, pertussis was one of the most common infectious causes of morbidity and death. In the United States prior to the 1940s, between 115,000 and 270,000 cases of pertussis were reported annually, with an average yearly rate of 150 cases per 100,000 population. With universal childhood immunization, the number of reported cases fell by >95%, with even more dramatic decreases in mortality. Only 1010 cases of pertussis were reported in 1976. Since that time, however, rates have slowly increased. In 1994, over 15,000 cases of pertussis were reported in the United States.

Although thought of as a disease of childhood, pertussis can affect people of all ages and is increasingly being identified as a cause of prolonged coughing illness in adolescents and adults. In unimmunized populations, pertussis incidence peaks in the preschool years, and well over half of children have the disease before reaching adulthood. In highly immunized populations such as those in North America, the peak incidence is in infants <1 year of age who have not completed the three-dose primary immunization series. Recent trends, however, show an increasing incidence of pertussis in adolescents and adults. In the United States in 1997, ~30% of patients were £6 months of age, 25% were adolescents, and 20% were adults. The figures for adolescents and adults are probably underestimates because of a greater degree of underrecognition and underreporting in these age groups. A number of studies of prolonged coughing illness suggest that pertussis may be the etiologic agent in 12 to 30% of adults with cough that does not improve within 2 weeks. A seroprevalence study in the United States estimated an annual incidence of pertussis of 176 cases per 100,000 healthy adults. This high incidence undoubtedly includes subclinical and mild cases that would not be readily identified as pertussis; this fact accounts for infection rates similar to those reported before the introduction of routine immunization.

Severe morbidity and mortality, however, are virtually restricted to infants. In Canada, there were 10 deaths from pertussis between 1991 and 1998; all those who died were infants£6 months of age. Although school-age children are the source of infection for most households, adults are the likely source for high-risk infants and may serve as the reservoir of infection between epidemic years. In developing countries, pertussis remains an important cause of infant morbidity and mortality. The World Health Organization estimated that in 1995 over 40 million people worldwide were infected by *B. pertussis* and that 355,000 children died of pertussis.

## CLINICAL MANIFESTATIONS

Pertussis is a prolonged coughing illness with clinical manifestations that vary by age (Table 152-1). Classic pertussis is most often seen in preschool and school-age children, although it is not uncommon among adolescents and adults. After an incubation period averaging 7 to 10 days, an illness develops that is indistinguishable from the common cold and is characterized by coryza, lacrimation, mild cough, low-grade fever, and malaise. After 1 to 2 weeks, this *catarrhal phase* evolves into the *paroxysmal phase*: the cough becomes more frequent and spasmodic with repetitive bursts of 5 to 10 coughs, often within a single expiration. Posttussive vomiting is frequent, with a mucous plug occasionally expelled at the end of an episode. The episode may be terminated by an audible whoop, which occurs upon rapid inspiration against a closed glottis at the end of a paroxysm. During a spasm, there may be impressive neck-vein distension, bulging eyes, tongue protrusion, and cyanosis. Paroxysms may be precipitated by noise, eating, or physical contact. Between attacks, the patient's appearance is normal but increasing fatigue is evident. The frequency of paroxysmal episodes varies widely, from several per hour to 5 to 10 per day. Episodes are often worse at night and interfere with sleep. Weight loss is not uncommon as a result of interference with eating. Most complications occur during the paroxysmal stage. Fever is uncommon and suggests bacterial superinfection.

After 2 to 4 weeks, the coughing episodes become less frequent and less severe -- changes heralding the onset of the *convalescent phase*. This phase can last from 1 to 3 months and is characterized by a gradual resolution of the coughing episodes. For 6 months to a year, intercurrent viral infections may be associated with a recrudescence of paroxysmal cough.

Not all children who develop pertussis have classic disease. Although cough (typically paroxysmal) is nearly always present, whoop may occur in only half of cases. In infants, the illness may be atypical; often apnea and cyanosis are the only symptoms at presentation. Seizures, encephalopathy, and pneumonia are all more common in infants£6 months old. Pertussis-associated infant deaths due to apnea may be confused with sudden infant death syndrome. The clinical manifestations in adolescents and adults may be classic but are more often atypical. In a German study of pertussis in adults, over two-thirds had paroxysmal cough and over one-third had whoop. Adult illness in North America differs from this experience: the cough may be severe and prolonged but is less frequently paroxysmal, and a whoop is uncommon. Vomiting with cough is the best predictor of pertussis as the cause of a prolonged cough in adults. Other features predictive of the disease are a cough at night and exposure to other individuals with a prolonged coughing illness.

## COMPLICATIONS

Complications are frequently associated with pertussis and are more common among infants than among older children or adults. Subconjunctival hemorrhages, abdominal and inguinal hernias, pneumothoraces, and facial and truncal petechiae can result from increased intrathoracic pressure generated by severe fits of coughing. Weight loss can follow decreased caloric intake. In a series of over 1100 children <2 years of age who were hospitalized with pertussis, 27.1% had apnea, 9.4% had pneumonia, 2.6% had seizures, and 0.4% had encephalopathy; 10 children (0.9%) died. Pneumonia is

reported in fewer than 5% of adolescents and adults and is usually caused by encapsulated organisms such as *Streptococcus pneumoniae* or *Haemophilus influenzae*; in contrast, infants develop primary *B. pertussis* pneumonia. Pneumothorax, severe weight loss, inguinal hernia, rib fracture, and cough syncope have all been reported in adolescents and adults with pertussis.

## DIAGNOSIS

If the classic symptoms of pertussis are present, clinical diagnosis is not difficult. However, particularly in older children and adults, it is difficult to differentiate infections caused by *B. pertussis* and *B. parapertussis* from other respiratory tract infections on clinical grounds. Therefore, laboratory confirmation should be attempted in all cases. Lymphocytosis (absolute neutrophil count, >10´$10^9$/L) is common among young children (in whom it is unusual with other infections) but not among adolescents and adults. Culture of nasopharyngeal secretions remains the "gold standard" of diagnosis; the best specimen is collected by nasopharyngeal aspiration, in which a fine flexible plastic catheter attached to a 10-mL syringe is passed into the nasopharynx and withdrawn while gentle suction is applied. Since *B. pertussis* is highly sensitive to drying, secretions should be inoculated without delay onto appropriate media (Bordet-Gengou or Regan-Lowe) or the catheter should be flushed with a phosphate-buffered saline solution. An alternative is a nasopharyngeal culture with a calcium alginate swab; again, inoculation of culture plates should be immediate or an appropriate transport medium (such as Regan-Lowe charcoal medium) should be used. Cultures become positive by day 5 of incubation, and *B. pertussis* and *B. parapertussis* can be differentiated by agglutination with specific antisera or by direct immunofluorescence.

Nasopharyngeal cultures in untreated pertussis remain positive for a mean of 3 weeks after the onset of illness; these cultures become negative within 5 days of the institution of appropriate antimicrobial therapy. Since much of the period during which the organism can be recovered from the naropharynx falls in the catarrhal phase, when the etiology of the infection is not suspected, there is only a small window of opportunity for culture-proven diagnosis. Cultures from infants and young children are more frequently positive than those from older children and adults; this difference may reflect earlier presentation of the former age group for medical care. The increasing availability of the polymerase chain reaction for pertussis in diagnostic laboratories is enhancing the sensitivity of the organism's detection. This method may further laboratory confirmation but does not solve problems related to the long delays in specimen procurement that often are encountered in pertussis cases. Direct fluorescent antibody tests of nasopharyngeal secretions for direct diagnosis may still be available in some laboratories but should not be used because of poor sensitivity and specificity.

As a result of the difficulties with laboratory diagnosis of pertussis in adolescents, adults, and any patient who has been symptomatic for >4 weeks, increasing attention is being given to serologic diagnosis. Enzyme immunoassays detecting IgA and IgG antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae have been developed and assessed for their reproducibility. Two- or fourfold increases in antibody are suggestive of pertussis, although cross-reactivity of some antigens (such as filamentous hemagglutinin) among *Bordetella* species makes it difficult to depend diagnostically on seroconversion involving a single type of antibody. Late presentation

for medical care and prior immunization also complicate serologic diagnosis because the first sample obtained may in fact be a convalescent-phase specimen. Proposed criteria for serologic diagnosis based on a single serum specimen call for comparison of the patient's antibody levels with established population values; for example, a patient with serologically confirmed pertussis might be required to have a titer greater than two or three standard deviations above the mean titer for a normal population. However, at present, no antibody test is widely or commercially available, and no specific serologic criteria are universally accepted.

## DIFFERENTIAL DIAGNOSIS

A child presenting with paroxysmal cough, posttussive vomiting, and whoop is likely to have an infection caused by *B. pertussis* or *B. parapertussis*; lymphocytosis increases the likelihood of a *B. pertussis* etiology. Viruses such as respiratory syncytial virus and adenovirus have been isolated from patients with clinical pertussis but probably represent co-infection. In adolescents and adults, among whom paroxysmal cough and whoop are frequently absent, the differential diagnosis of a prolonged coughing illness is more extensive. Pertussis should be suspected in anyone with a cough that does not improve within 14 days, a paroxysmal cough of any duration, or any respiratory symptoms after contact with a laboratory-confirmed case of pertussis. Other etiologies to consider include infections caused by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, adenovirus, influenza virus, and other respiratory viruses. Use of angiotensin-converting enzyme (ACE) inhibitors, reactive airway disease, and gastroesophageal reflux disease are well-described noninfectious causes of prolonged cough in adults.

## TREATMENT

**Antibiotics** The purpose of antibiotic therapy for pertussis is to eradicate the infecting bacteria from the nasopharynx; therapy does not substantially alter the clinical course unless given early in the catarrhal phase. Erythromycin (preferably the estolate form) is recommended at a dose of 50 mg/kg (maximum, 2 g/d) in three divided doses and reliably clears *B. pertussis* from the nasopharynx after 5 days. A dose of 1 g/d has also been shown to be effective and may be better tolerated. Although a 14-day course of therapy has been recommended to prevent relapse, one study showed that a 7-day course was equally effective. Erythromycin is also effective against other pathogens implicated in cough illness, such as *Mycoplasma* and *Chlamydia*.

Other macrolide antibiotics, such as azithromycin and clarithromycin, are active against *B. pertussis* in vitro, but data on their clinical efficacy are limited; clinical trials are under way. Trimethoprim-sulfamethoxazole (8/40 mg/kg per day in two divided doses) is recommended as an alternative for individuals who cannot use erythromycin, although good clinical data to support this recommendation are lacking. A macrolide-resistant *B. pertussis* strain has been reported from a single case in an outbreak in Arizona.

**Immune Globulin** Although immune globulin was used widely to treat pertussis in the preantibiotic era, evidence for its effectiveness was lacking and the commercially available product was removed from the market. There is renewed interest in the therapeutic use of immune globulin, particularly for infants who develop pertussis while

still too young to have completed their primary immunization series. A high-titer pertussis toxin immune globulin for intravenous use is undergoing clinical trials.

**Supportive Care** Infants have the highest rates of complication and death from pertussis; therefore, most infants and older children with severe disease should be hospitalized. Monitoring for apnea and cyanosis, administration of supplemental oxygen, management of secretions, hydration, and nutritional support are the mainstays of care. A quiet environment may decrease the stimulation that can trigger paroxysmal episodes. Assisted ventilation may be required for management of apnea or pneumonia. Use ofb-adrenergic agonists and/or glucocorticoids has been advocated by some but has not been proved to be effective. Cough suppressants are not effective and play no role in the management of pertussis.

**Infection Control Measures** Hospitalized patients with pertussis should be placed in respiratory isolation, with the use of precautions appropriate for pathogens spread by large respiratory droplets. Isolation should continue for 5 days after initiation of erythromycin therapy or for 3 weeks (i.e., until nasopharyngeal cultures are consistently negative) in those individuals unable to tolerate antimicrobial therapy.

## PREVENTION

**Chemoprophylaxis** Because the risk of transmission of *B. pertussis* within households is high, chemoprophylaxis is widely recommended for household contacts of pertussis cases. The effectiveness of chemoprophylaxis, although unproven, is supported by several epidemiologic studies of institutional and community outbreaks of pertussis. In the only randomized placebo-controlled study, erythromycin estolate (50 mg/kg per day in three divided doses; maximum dose, 1 g/d) was effective in reducing bacteriologically confirmed pertussis by 67%; however, there was no decrease in the incidence of clinical disease. Despite these disappointing results, many authorities continue to recommend chemoprophylaxis, particularly in households with members at high risk of severe disease (children<1 year of age). Data are not yet available on use of the newer macrolides for chemoprophylaxis.

**Immunization (See alsoChap. 122)** The mainstay of pertussis prevention is active immunization. Pertussis vaccine has been available for over 70 years and became widely used in North America after 1940; reported cases of pertussis have since fallen by >90%. Whole-cell pertussis vaccines are prepared through the heating, chemical inactivation, and purification of whole *B. pertussis* organisms. Although effective (average efficacy estimate, 85%, with results in various studies of different products ranging from 30 to 100%), whole-cell pertussis vaccines are associated with adverse events -- both common (fever; injection site pain, erythema, and swelling; irritability) and uncommon (febrile seizures, hypotonic hyporesponsive episodes). Alleged associations of whole-cell pertussis vaccine with encephalopathy, sudden infant death syndrome, and autism, although not substantiated, have spawned an active anti-immunization lobby. The development of acellular pertussis vaccines, which are effective but less reactogenic, has greatly alleviated concerns about the inclusion of pertussis vaccine in the combined infant immunization series. In some countries (Canada, Sweden, Germany), acellular pertussis vaccines are used exclusively for childhood immunization; in the United States, acellular pertussis vaccines are now the preferred product but

whole-cell vaccine is still considered acceptable. In North America, both whole-cell and acellular pertussis vaccines are given as a three-dose primary series at 2, 4, and 6 months of age, with a reinforcing dose between 15 and 18 months of age and a booster dose at 4 to 6 years of age.

A wide variety of acellular pertussis vaccines have been developed, although not all are available in every country. All acellular pertussis vaccines currently available contain pertussis toxoid. Only one monovalent pertussis toxoid vaccine has been licensed in the United States; the remainder of the fully developed vaccines contain filamentous hemagglutinin as well as toxoid. At least four acellular pertussis vaccines also contain pertactin, and two products also contain one or more types of fimbriae. All of the licensed acellular pertussis vaccines have undergone phase 3 efficacy testing. Although differences in study design make direct comparisons difficult, an effort to standardize case definitions and the similarity of some of the studies, which used common vaccine arms to allow "bridging" of the data between studies, have permitted some general conclusions. Even though some would still disagree, most experts have concluded that two-component acellular pertussis vaccines are more effective than monocomponent vaccines and that the addition of pertactin further increases efficacy. The further addition of fimbriae appears to provide some additional protective efficacy against milder disease. In two studies, protection against pertussis by vaccines correlated best with the production of antibody to pertactin, fimbriae, and pertussis toxin.

The development of acellular pertussis vaccines has sparked interest in the potential for control of pertussis in adolescents and adults and in the possibility that pertussis control in those groups will enhance the protection of infants too young to be immunized. Whole-cell pertussis vaccine is contraindicated in individuals³7 years of age because of their poor toleration of possible adverse events. However, adult formulations of acellular pertussis vaccines, both alone and in combination with adult-formulation diphtheria-tetanus toxoid, have been demonstrated to be safe and immunogenic in clinical trials in adolescents and adults. Further epidemiologic studies and an efficacy study are under way to better delineate the scope of pertussis illness in adolescents and adults as well as the efficacy of a single dose of acellular pertussis vaccine. These data, along with the results of other studies characterizing the spectrum of pertussis disease in adolescents and adults, will help public health authorities and advisory committees to determine the role of adolescent and adult pertussis immunization.

(Bibliography omitted in Palm version)

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Back to Table of Contents

# 153. DISEASES CAUSED BY GRAM-NEGATIVE ENTERIC BACILLI - *Thomas A. Russo*

## GENERAL FEATURES AND PRINCIPLES

### EPIDEMIOLOGY

This chapter discusses gram-negative bacilli (GNB) belonging to the medically important genera of the family Enterobacteriaceae (*Escherichia*, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, and *Edwardsiella*) as well as the genus *Actinetobacter* from the family Neisseriaceae. These bacteria are members of normal animal and human colonic flora and/or residents of a variety of environmental habitats, including long-term-care facilities and hospitals. In healthy humans, *Escherichia coli* is the predominant species of GNB in the colonic flora. GNB (primarily *E. coli*, *Klebsiella*, and *Proteus*) only transiently colonize the oropharynx and skin. In contrast, in the long-term-care and hospital settings, a variety of GNB emerge as the dominant components of the colonizing flora of both mucosal and skin surfaces, particularly with antimicrobial use and increasing severity of disease. Acquisition of these GNB from a variety of reservoirs leads to infection.

### STRUCTURE AND FUNCTION

Structurally, these organisms possess an extracytoplasmic outer membrane, a feature shared among gram-negative bacteria. The outer membrane consists of a lipid bilayer and associated proteins, lipoproteins, and polysaccharides [capsule, lipopolysaccharide (LPS)]. This structure interfaces with the environment, including the human host. A variety of components of the outer membrane are critical determinants in mediating the pathogenesis of infection and antimicrobial resistance.

### INFECTIOUS SYNDROMES

Depending on both the host and the pathogen, nearly every organ and body cavity can be infected withGNB. *Escherichia* and, to a lesser degree, *Klebsiella* and *Proteus* account for the majority of infections and are the most virulent pathogens of this group. However, the other genera are becoming increasingly important, particularly in long-term-care or hospitalized patients, in large part because of the organisms' innate or acquired resistance to antimicrobial agents and the increasing number of immunocompromised hosts. The mortality rate is significant in many GNB infections and correlates with the severity of illness. Especially problematic are pneumonitis and bacteremia from any source complicated by shock, which have associated mortality rates of 20 to 50%.

### DIAGNOSIS

Isolation of GNBfrom sterile sites almost always implies infection. Their isolation from nonsterile sites, particularly from soft tissue and respiratory cultures, requires clinical correlation to differentiate colonization from infection.

### TREATMENT AND PREVENTION

The antimicrobial resistance ofGNB is variable and is influenced by both location and regional antibiotic use. Empirical antimicrobial choices should be based on local susceptibility patterns, but it is critical to be cognizant of emerging resistance. The acquisition of transferable plasmids that possess genes for extended-spectrumb-lactamases (ESBLs) is increasing. To date, these plasmids are most prevalent in *Klebsiella* and *E. coli*, but they have also been described (albeit less frequently) in most of the enteric GNB. The plasmids confer resistance to third-generation cephalosporins and aztreonam and frequently contain linked resistance determinants for aminoglycosides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMZ). In some outbreaks, strains with ESBLs also exhibit associated fluoroquinolone resistance. Derepression of inducible chromosomal b-lactamases, another important resistance mechanism, may be preexisting or may develop during therapy. This determinant confers resistance to second- and third-generation cephalosporins, to aztreonam, and often tob-lactam/b-lactamase inhibitor combinations. Of the enteric GNB, *Enterobacter*, *Serratia*, *Citrobacter*, *Proteus vulgaris*, *Proteus penneri*, *Providencia*, and *Morganella* possess this determinant. Although relevant data are suboptimal or conflicting, combination therapy may increase antimicrobial efficacy (particularly in serious infections, such as pneumonitis) and diminish the emergence of resistance. Further, drainage of abscesses and removal of infected foreign bodies are often needed for cure. GNB are commonly part of a polymicrobial infection in which it is difficult to determine the role of each specific pathogen. Although some species are more pathogenic than others, it is usually prudent, if possible, to design an antimicrobial regimen that includes activity against all of the GNB identified, since each is capable of pathogenicity in its own right. Diligent hand washing by health care personnel and avoidance of inappropriate antimicrobial use are the two most important measures for the prevention of infection.

## PATHOGENESIS

Multiple bacterial traits are required for various aspects of the pathogenesis ofGNB. The possession of specialized virulence genes is what defines pathogens and enables them to infect the host efficiently. As more is learned about these genes, it is becoming clear that hosts and their cognate pathogens have been coadapting throughout evolutionary history. In fact, it has been speculated that infection is just a point on the spectrum of evolutionary development between microbes and the host. At one end of this spectrum is a commensal/symbiotic interaction (e.g., mitochondria -- formerly bacteria -- within eukaryotic cells); at the other is a lethal outcome that results in a "dead-end relationship" (e.g., Ebola virus). During this host-pathogen "chess match" over time, a variety and redundancy of solutions have emerged in both pathogens and hosts that enable the partners to maintain their coexistence (Table 153-1).

**Intestinal Infection** Intestinal pathogenic strains of *E. coli* cause gastroenteritis by a variety of unique pathogenic mechanisms. Their virulence traits are for the most part distinct from those of *E. coli* strains that cause disease outside the bowel. This difference is not surprising in light of site-dependent differences in host environments and defense mechanisms.

**Extraintestinal Infection** Extraintestinal pathogenic strains of *E. coli* (ExPEC) and the

other genera discussed in this chapter cause infection outside the bowel. All are extracellular pathogens and therefore share certain pathogenic features. Innate defense systems (complement, phagocytes) and humoral immunity are the most critical host defense components. As a result, both susceptibility to and severity of infection are increased with dysfunction or deficiencies of these components (e.g., neutrophils). A given pathogen usually possesses multiple adhesins for binding to a variety of host cells (e.g., in *E. coli*: type I, Sfa/Foc, P pili). Nutrient acquisition (e.g., iron via siderophores) requires many genes that are necessary but not sufficient for pathogenesis. The ability to resist the bactericidal activity of complement and professional phagocytes in the absence of antibody (e.g., conferred by capsule or O antigen ofLPS) is one of the defining traits of an extracellular pathogen. Tissue damage (e.g., hemolysis in the case of *E. coli*) may facilitate spread. However, many important virulence genes await identification, and our understanding of many aspects of the pathogenesis ofGNB is in its infancy (Chap. 120). The ability to induce septic shock is another defining feature of these genera. GNB are the most common cause of this dangerous complication. The lipid A moiety of LPS and probably other bacterial factors as well (e.g., capsule) stimulate a proinflammatory host response, which, if overexuberant, results in shock (Chap. 124). Lastly, a large number of serotypes (e.g., in *E. coli*, >100 O-specific and>80 capsular antigens) exist within most genera of GNB. This antigenic variability enables immune evasion and successful recurrent infection by strains of the same species and has also impeded vaccine development (Chap. 122).

## *ESCHERICHIA COLI* INFECTIONS

From a clinical perspective, *E. coli* can be divided into three categories: commensal strains, intestinal pathogenic (enteric or diarrheagenic) strains, andExPEC.

### ETIOLOGY, EPIDEMIOLOGY, AND MANIFESTATIONS

**Commensal Strains** Commensal strains of *E. coli* constitute the bulk of the facultative fecal flora in most healthy humans. Such strains appear to be adapted for peaceful coexistence with the host and appear not to cause disease within the intestinal tract. Further, in humans, these microorganisms do not usually cause disease outside the intestinal tract except in the presence of precipitating factors, such as an indwelling foreign body or an impairment of host defenses. Commensal *E. coli* strains typically lack the specialized virulence traits of intestinal andExPECstrains.

**Intestinal Pathogenic Strains** In contrast to commensal *E. coli*, intestinal pathogenic strains of *E. coli* are rarely encountered in the fecal flora of healthy hosts and instead appear to be essentially obligate pathogens, causing gastroenteritis or colitis whenever ingested in sufficient quantities by a naive host. At least six distinct "pathotypes" of intestinal pathogenic *E. coli* exist: (1) enterotoxigenic *E. coli* (ETEC); (2) Shiga toxin-producing *E. coli* (STEC)/enterohemorrhagic *E. coli* (EHEC); (3) enteropathogenic *E. coli* (EPEC); (4) enteroinvasive *E. coli* (EIEC); (5) enteroaggregative *E. coli* (EAEC); and (6) diffusely adherent *E. coli* (DAEC). Organisms of these pathotypes are acquired via the fecal-oral route. Transmission occurs predominantly via contaminated food and water for ETEC, STEC, EIEC, EAEC, and DAEC and by person-to-person spread for EPEC (and occasionally STEC). Humans appear to be the major reservoir (except for STEC), since the host range appears to be dictated by species-specific attachment

factors. Although there is some overlap, each pathotype possesses a unique combination of virulence traits that results in a distinctive intestinal pathogenic mechanism; however, these strains are largely incapable of causing disease outside the intestinal tract.

*ETEC*In tropical or developing countries, several separate episodes of ETEC infection occur in children over the first 3 years of life. The incidence of disease diminishes with age, a pattern suggesting the development of immunity. In industrialized countries, infection usually follows travel to endemic areas. ETEC is the most common cause of traveler's diarrhea (Chap. 123), being responsible for 25 to 75% of cases. Cases usually develop within the first few weeks of travel. The incidence of infection is decreased by the prudent avoidance of potentially contaminated fluids and foods. ETEC infection is uncommon in the United States, but outbreaks have taken place secondary to contamination of domestic food products. A high inoculum ($10^6$ to $10^{10}$CFU) is needed to cause disease. After ingestion of contaminated water or food (particularly items poorly cooked, unpeeled, or unrefrigerated), the small bowel is colonized during a 1- to 7-day incubation period. Disease is mediated in part by heat-labile (LT) and/or heat-stable (STa) toxin encoded by genes present on transferable plasmids. These toxins stimulate fluid secretion via activation of adenylate cyclase (LT) and/or guanylate cyclase (STa); the result is watery diarrhea accompanied by cramps. Characteristically absent are histopathologic changes of the small bowel; mucus, blood, and inflammatory cells in stool; and fever. The disease spectrum ranges from mild illness to a life-threatening cholera-like illness. Although symptoms are usually self-limited (2 to 6 days), infection may result in significant morbidity and mortality when health care is poor and small and/or undernourished children are affected.

*STEC*/*EHEC*STEC strains constitute an emerging group of pathogens that have received substantial media attention as a result of several large outbreaks attributable to the consumption of undercooked ground beef and other foods. Serotype O157:H7 is the most prominent of the more than 30 serotypes associated with the STEC syndrome (see below). Other common serogroups include O26, O39, O103, O104, and O111. The ability to produce Shiga-like toxin (Stx2 and/or Stx1) or related toxins is the critical factor dictating whether a bacterium can cause the clinical syndrome associated with STEC. *Citrobacter* isolates that produce Stx2 and *Shigella* strains that produce related toxins can cause the same syndrome.

A combination of factors are responsible for the emergence ofSTECdisease. A number of animals, including cattle and young calves, serve as a major reservoir for these strains. Ground beef, the most common food source, is frequently contaminated during processing. Further, cattle or other animal manure used as fertilizer can contaminate produce (potatoes, lettuce, sprouts, fallen apples) and water (fecal runoff). It is estimated that$<10^3$CFU of STEC can cause disease. Therefore, not only can low levels of food or environmental contamination (e.g., water swallowed when swimming) result in disease, but person-to-person transmission becomes an important vehicle for secondary spread (e.g., at day-care centers and in institutions). Because of the low infective dose (which is similar to that of *Shigella*), laboratory-associated infections also take place. Both outbreaks and sporadic disease occur with this group of pathogens, with a seasonal peak in the summer.

In contrast to infection with the other five pathotypes, infection withSTECoccurs more frequently in developed countries, where consumption of processed foods is more common than in developing regions. FoodNet data indicate that O157 strains are the fourth most common reported cause of bacterial diarrhea in the United States (behind *Campylobacter*, *Salmonella*, and *Shigella*). Colonization of the colon and perhaps of the ileum results in symptoms after an incubation period of 3 or 4 days. Maximal disease expression requires Stx2 (produced by most O157 isolates) and/or Stx1 (more commonly produced by non-O157 isolates) as well as other virulence genes (e.g., *eaeA*). Colonic edema and an initial secretory diarrhea may develop into the syndrome's hallmark trait of grossly bloody diarrhea (detected by history or examination) in >90% of cases. Significant abdominal pain and fecal leukocytes are commonly present (70% of cases), but fever is usually absent. Occasionally, *Clostridium difficile*, *Campylobacter*, and *Salmonella* infection present in a similar fashion, as do noninfectious diseases (e.g., appendicitis, inflammatory bowel disease). STEC disease is usually self-limited, lasting 5 to 10 days. This infection can be complicated by the hemolytic-uremic syndrome (HUS), which occurs 2 to 14 days after diarrhea in 2 to 8% of cases, most often in the very young and the elderly. An estimated 50% of all cases of HUS in the United States are caused by STEC infection. This complication is probably mediated by the systemic translocation of Shiga-like toxins and subsequent cellular damage, particularly to endothelial cells in the renal and cerebral microvasculature. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Neurologic symptoms, with or without fever, can also occur. Although mortality with dialysis support is <10%, residual renal dysfunction and neurologic sequelae may persist.

*EPEC*EPEC causes disease primarily in young children, including neonates. This *E. coli* group was recognized as a cause of diarrheal disease when it was found in outbreaks of infantile diarrhea (some in hospital nurseries) in industrialized countries in the 1940s and 1950s. Presently, however, infection due to EPEC is uncommon in developed countries. In contrast, EPEC is an important cause of infant diarrhea (both sporadic and epidemic) in developing countries. Breast-feeding diminishes the incidence of infection. Rapid person-to-person spread may occur. Upon colonization of the small bowel, symptoms develop after an incubation period of 1 or 2 days. Disease is not toxin-mediated. Studies have identified a variety of virulence traits responsible for adherence and a characteristic effacement of microvilli with formation of cuplike, actin-rich pedestals to which the bacteria attach. Diarrheal stool often contains mucus but not blood. Although usually self-limiting, EPEC diarrhea may persist for weeks.

*EIEC*EIEC is a relatively uncommon cause of diarrhea and is rarely identified in the United States, although a few food-related outbreaks have been described. In less developed countries, sporadic disease is infrequently recognized in children and travelers. EIEC shares many features with *Shigella* infection; however, unlike *Shigella*, EIEC causes disease only at a high inoculum ($10^8$ to $10^{10}$CFU). Invasion of and replication within the colonic mucosa result in the development of symptoms after an incubation period of 1 to 3 days. Secretory diarrhea may evolve into inflammatory colitis characterized by fever, abdominal pain, tenesmus, and scant stool containing mucus, blood, and inflammatory cells. Symptoms are usually self-limited, lasting 7 to 10 days.

*EAEC*and*DAEC*These pathotypes have been described primarily in developing countries and mostly affect young children. These strains may also cause some cases

of traveler's diarrhea. A high inoculum is required for infection. In vitro, the organisms exhibit a diffuse or "stacked-brick" adherence pattern. Clinical disease has been associated with persistent diarrhea.

## DIAGNOSIS

A practical approach in evaluating diarrhea is to distinguish noninflammatory from inflammatory cases (Chap. 131).ETEC,EPEC,EAEC, and DAECare uncommon causes of noninflammatory diarrhea in the United States. Their diagnosis requires specialized assays that are not routinely available and whose use is rarely indicated since these diseases are self-limiting. ETEC causes the majority of cases of noninflammatory traveler's diarrhea; EAEC and DAEC cause a minority of these cases. Definitive diagnosis generally is not necessary, and empirical antimicrobial treatment is a reasonable approach. If diarrhea persists with treatment, *Giardia* or *Cryptosporidium* should be sought. The diagnosis of infection withEIEC, a rare cause of inflammatory diarrhea in the United States, also requires specialized assays. However, evaluation forSTEC, particularly when bloody diarrhea is reported or observed, is appropriate. Although screening for *E. coli* strains that do not ferment sorbitol and subsequent serotyping for O157 constitute the most common method presently used to detect STEC, testing for Shiga-like toxins or toxin genes is more sensitive, specific, and rapid. The latter approach offers another advantage: it detects both non-O157 strains and sorbitol-fermenting strains of O157, which otherwise are difficult to identify. DNA-based, enzyme-linked immunosorbent, and cytotoxicity assays are in various stages of development and will probably become the diagnostic standards in time.

**Extraintestinal Pathogenic Strains** From both pathogenic and clinical viewpoints,ExPECstrains are distinct from commensal and intestinal pathogenic strains of *E. coli*. ExPEC strains also make up part of the normal human fecal flora, but, in contrast to commensal strains, possess specialized genes that encode virulence factors enabling the organisms to cause extraintestinal infections (Table 153-1). ExPEC (as opposed to commensal *E. coli*) causes the majority of cases of urinary tract infection (UTI), bacteremia, and neonatal meningitis. It is likely that ExPEC also causes the majority of other extraintestinal infections due to *E. coli*. Entry into an extraintestinal site (e.g., the urinary tract or the peritoneum) -- not acquisition -- is the limiting factor for infection. All age groups, all types of hosts, and nearly every organ and site are susceptible to infection by ExPEC. Normal, previously healthy hosts infected with ExPEC can become severely ill and die. However, adverse outcomes are more prevalent in the presence of coincidental disease and abnormalities in host defenses. Typical extraintestinal infections include UTI, diverse intraabdominal infections, pneumonia (particularly in hospitalized and institutionalized patients), meningitis (mainly in neonates and patients who have undergone neurosurgery), intravascular device infection, osteomyelitis, and soft tissue infection (which usually occurs in the setting of tissue compromise). Bacteremia can accompany infection at any of these sites. Although *E. coli* is considered to be primarily a community-acquired pathogen, it is the most frequently isolated of theGNB in the ambulatory, long-term-care, and hospital settings. The scope and magnitude of infection caused by ExPEC are as great as for any other invasive bacterial pathogen. Although these isolates do not make headlines, billions of health care dollars, millions of workdays, and thousands of lives are lost to this group of pathogens each year.

*URINARY TRACT INFECTION (UTI)* The urinary tract is the site most frequently infected byExPEC. About 90% of ambulatoryUTIs and 25 to 35% of long-term-care and hospital UTIs are due to *E. coli*. The majority of UTIs occur in seven epidemiologically defined groups: children<1 year of age, school-age girls, premenopausal women, men with prostatic or other causes of urinary tract obstruction, postmenopausal women, individuals with neurogenic bladders, and patients with indwelling urinary catheters. In premenopausal women, diaphragm-spermicide use, sexual activity, and a history of UTI are risk factors for infection; 20% of women with an initial infection have frequent recurrences (0.3 to>20 per year). In postmenopausal women, estrogen replacement decreases the incidence of UTI. Acceptance of the diagnosis of UTI in males (beyond the first year of life) requires clear documentation since this infection is unusual in the absence of a history of instrumentation or anal intercourse. UTI in premenopausal women alone accounts for an estimated 7 million office visits and >$1 billion in direct medical costs annually. UTI is the second most common infection (behind lower respiratory tract infection) responsible for hospitalization.

Uncomplicated urethritis or cystitis occurs most commonly and is characterized by symptoms of dysuria, frequency, and suprapubic pain. Fever and/or back pain suggests progression to pyelonephritis. Pregnant women are at unusually high risk for this complication, which can adversely affect the outcome of pregnancy. As a result, prenatal screening for bacteriuria, with treatment when the results are positive, is the standard of care. Fever may take 5 to 7 days to resolve completely in appropriately treated patients with pyelonephritis but should fall over time. Persistently elevated or increasing fever and neutrophil counts should prompt evaluation for intrarenal or perinephric abscess and/or obstruction. Renal parenchymal damage and loss of renal function occur primarily in the setting of obstruction. Prostatic infection is generally a complication ofUTI in men with a history of instrumentation and/or prostatic hypertrophy. The diagnosis and treatment of UTI are detailed inChap. 280 and are tailored according to the host, the nature and site of infection, and the local pattern of antimicrobial susceptibility.

*ABDOMINAL INFECTION* The abdomen is the second most frequent site of extraintestinal infection due to *E. coli*. The majority of abdominal *E. coli* infections develop outside the hospital. Any inciting event that results in disruption of the bowel mucosa (particularly the colonic mucosa) often leads to acute peritonitis (secondary peritonitis; Chap. 130). This process is usually polymicrobial, but *E. coli* is isolated in most cases. Bacteremia often complicates this acute stage of infection. Abscess formation within the peritoneum may follow the acute stage or may develop as a consequence of subclinical fecal spillage (e.g., diverticulitis, chronic appendicitis). Intraperitoneal abscesses are almost always polymicrobial, with *E. coli* as the most commonGNBisolated. *E. coli* is also the GNB most often responsible for primary hepatic abscesses, hepatic abscesses in the setting of biliary disease and obstruction, septic cholangitis/cholecystitis, pancreatic abscesses, and infected pancreatic pseudocysts. This organism is the leading cause of spontaneous bacterial peritonitis, usually seen in patients who have ascites associated with cirrhosis or occasionally with malignancy. *E. coli* occasionally causes splenic abscesses and peritoneal dialysis-associated peritonitis

(Chap. 130).

*PNEUMONIA E. coli* is not usually considered a cause of pneumonia (Chap. 255). EntericGNB are responsible for only 2 to 5% of cases of community-acquired pneumonia, in part because these organisms only transiently colonize the oropharynx in a minority of healthy individuals. In contrast, oral colonization with *E. coli* and other GNB increases with the severity of illness and with antibiotic use. Thus, GNB are a common cause of pneumonia acquired by residents of long-term-care institutions and are the most frequent cause of hospital-acquired pneumonia (Chap. 135), particularly in postoperative and intensive care patients. Despite significant institutional variation, *E. coli* is generally the third or fourth most commonly isolated GNB in these settings, behind *Pseudomonas* and *Klebsiella*. Regardless of the host, severe disease and high mortality rates (20 to 60%) are usually seen when GNB cause pneumonia. Tissue necrosis, probably due to cytotoxins produced by GNB, is common. Infection is usually acquired by small-volume aspiration but occasionally occurs via hematogenous spread, in which case multifocal nodular infiltrates can be seen.

*MENINGITIS (SeeChap. 372)* ExPECare a leading cause of meningitis in the first month of life. The majority of responsible strains possess the K1 capsular serotype. Outside this setting, meningitis due to *E. coli* is uncommon, occurring predominantly with cirrhosis (Chap. 299) or disruption of the meninges due to surgery or trauma.

*CELLULITIS/MUSCULOSKELETAL INFECTION* Infections of decubitus ulcers and the lower extremities in diabetic patients (or other hosts with neurovascular compromise) are usually polymicrobial. *E. coli* frequently contributes to infection of decubiti and occasionally to lower-extremity infections in these patients. It may occasionally cause cellulitis or burn site or surgical wound infection, particularly when the infection originates close to the perineum. Osteomyelitis secondary to contiguous spread can occur in these settings. Hematogenously acquired osteomyelitis, particularly of vertebral bodies, is more common than is appreciated, accounting for 10% of cases in some series (Chap. 129). *E. coli* occasionally causes orthopedic device-associated infection and is a rare cause of hematogenously acquired myositis. Myositis or fasciitis of the upper leg should prompt an evaluation for an abdominal source with contiguous spread.

*ENDOVASCULAR INFECTION* Extraintestinal isolates of *E. coli* cause a significant minority of intravascular device-associated infections (Chap. 135). Despite being one of the most common causes of bacteremia, however, *E. coli* rarely seeds native heart valves and is an uncommon cause of prosthetic valve endocarditis. Likewise, *E. coli* infections of aneurysms and vascular grafts are uncommon.

*MISCELLANEOUS INFECTIONS E. coli* can cause infection in nearly every organ and site. This organism causes a minority -- but still a significant number -- of surgical site infections (e.g., mediastinitis) and cases of complicated sinusitis. It uncommonly causes endophthalmitis.

*BACTEREMIA E. coli* bacteremia can result from extraintestinal infection of any site. The incidences of community-acquired and long-term-care/hospital-acquired bacteremia are roughly equal. Overall, it has been amply documented that *E. coli* and *Staphylococcus aureus* are the most common blood isolates (range for *E. coli*, 16 to

37%). *E. coli* is theGNB most frequently isolated from blood in the ambulatory setting and in most long-term-care and hospital settings. When *E. coli* is isolated from the blood, it is almost always clinically significant. Approximately 15% of bacteremias are complicated by septic shock. Two-thirds of bacteremias arise from the urinary tract; these infections are particularly common in the setting of pyelonephritis or obstruction (including kinked urinary catheters) or instrumentation of the urinary tract in the presence of *E. coli*. However, one should be cautious in identifying the urinary tract as the source of *E. coli* bacteremia in the absence of appropriate symptoms, despite a positive urine culture. Asymptomatic bacteriuria is common, particularly in women, even in the absence of an indwelling bladder catheter, with a prevalence of 15 to 25% after the age of 60. Therefore, occult abdominal or other sources should be considered. The abdomen is the second most common source, accounting for 25% of episodes. Although obstructive biliary tract disease (stones, tumor) and overt disruption of the bowel are responsible for many cases of *E. coli* bacteremia, some abdominal sources, such as abscesses, are remarkably silent clinically and require identification via imaging studies (e.g., computed tomography). Soft tissue, bone, and pulmonary infection are the next most frequent sources for bacteremia. As stated above, endocarditis is uncommon, occurring in only 2 of 861 bacteremias in a recent series. In the setting of chemotherapy-induced fever and neutropenia, *E. coli* is a common cause of bacteremia, usually secondary to intestinal mucositis. It is prudent in this situation, however, to exclude perirectal infection or typhlitis (Chap. 89).ExPECstrains are among the most common causes of sepsis in neonates.

*Diagnosis* Strains of *E. coli* that cause extraintestinal infections usually grow both aerobically and anaerobically within 24 h on standard diagnostic media and are easily identified by the clinical microbiology laboratory using standard biochemical criteria (Chap. 121). More than 90% of these strains are rapid lactose fermenters.

## TREATMENT

Although *E. coli* is generally perceived as an "antibiotic-friendly" pathogen, resistance has increased over the past decade. In general, the frequency of ampicillin resistance precludes its empirical use, even in community-acquired infections. Rates of resistance to first-generation cephalosporins andTMP-SMZin community-acquired strains are increasing in the United States (5 to 25%) and are even higher in Europe and developing countries. Not surprisingly, long-term-care and hospital isolates are more resistant than community isolates. Significant resistance (30 to 40%) to amoxicillin/clavulanic acid and piperacillin has been increasingly reported. Fortunately, resistance to second- and third-generation cephalosporins [mean rate, 3.2% according to 1998 National Nosocomial Infections Study (NNIS) data], fourth-generation cephalosporins, quinolones, monobactams (e.g., aztreonam), carbapenems (e.g., imipenem), and aminoglycosides is generally found in <10% of strains. An exception is in settings where quinolone prophylaxis is used extensively (patients with leukemia, transplant recipients); in these settings, significant quinolone resistance has emerged. Acquisition of plasmids containingESBLsand other resistance determinants is likely to increase.

The mainstay of treatment for all diarrheal syndromes is the appropriate replacement of water and electrolytes (Chap. 159). The use of prophylactic antibiotics to prevent

traveler's diarrhea should be discouraged, especially in light of high rates of antibiotic resistance. When diarrhea is free of mucus and blood, early patient-initiated treatment with a quinolone significantly decreases the duration of illness, and the use of loperamide may halt symptoms in a few hours (Chap. 123). Treatment ofSTEC is controversial since antibiotics may increase the incidence ofHUS, perhaps via increased release of Shiga-like toxin.

## INFECTIONS CAUSED BY OTHER GRAM-NEGATIVE ENTERIC BACILLI

### *KLEBSIELLA* INFECTIONS

*K. pneumoniae* is the most important *Klebsiella* species medically, causing community-acquired, long-term-care, and hospital infections. *K. oxytoca* is primarily a pathogen in long-term-care and hospital settings. *K. rhinoscleromatis* and *K. ozaenae* are usually isolated from patients in tropical climates. *Klebsiella* species are broadly prevalent in the environment and colonize mucosal surfaces of mammals. In healthy humans, *K. pneumoniae* colonization rates range from 5 to 35% in the colon and from 1 to 5% in the oropharynx; the skin is usually colonized only transiently. In long-term-care facilities and hospitals, colonization occurs with *K. oxytoxa* as well, and carriage rates are significant among both workers and patients. Person-to-person spread is thought to be the predominant mode of acquisition. Classically, *Klebsiella* is associated with community-acquired pneumonia, primarily in alcoholics. However, the majority of *Klebsiella* infections now occur in long-term-care facilities and hospitals. *Klebsiella* causes a spectrum of extraintestinal infections similar to that caused by *E. coli*. However, extraintestinal infections due to *Klebsiella* occur at a lower incidence in all sites except the respiratory tract. These variances in infection rates are probably due to differences in colonization and site-specific virulence traits. Antibiotic-resistant strains have been responsible for a number of nosocomial outbreaks of infection in intensive care units (ICUs) and neonatal nurseries. The most common clinical syndromes are pneumonia,UTI, abdominal infection, surgical site infection, soft tissue infection, and subsequent bacteremia. *K. rhinoscleromatis* is the causative agent of rhinoscleroma, a slowly progressive (months to years) mucosal upper respiratory infection that causes necrosis and occasional obstruction of the nasal passages. *K. ozaenae* has been implicated as a cause of chronic atrophic rhinitis.

#### Infectious Syndromes

*Pneumonia K. pneumoniae* causes only a small proportion of cases of community-acquired pneumonia (Chap. 255). This infection occurs primarily in hosts with underlying disease, such as alcoholics, diabetics, and individuals with chronic lung disease. As in all pneumonias due to entericGNB, purulent sputum production and "airspace" disease on x-ray are typical. Presentation with earlier, less extensive infection is more common than that with the classic lobar infiltrate with a bulging fissure. Pulmonary necrosis, pleural effusion, and empyema occur with progression. Pulmonary infection in residents of long-term-care facilities and in hospitalized patients is especially frequent because of increased oropharyngeal colonization rates. Mechanical ventilation is an important risk factor.

*UTI*The incidence of *K. pneumoniae* UTI among healthy adults is only 1 to 2%.

However, in complicated UTIs (including those associated with indwelling bladder catheters), the incidence of *Klebsiella* infection increases to 5 to 17%.

*Abdominal Infection Klebsiella* causes a spectrum of abdominal infections similar to that caused by *E. coli* but is less frequently isolated from these infections.

*Other Infections Klebsiella* cellulitis or soft tissue infection occurs most frequently in devitalized tissue (e.g., decubitus ulcers, diabetes, burn sites) or in immunocompromised hosts. *Klebsiella* causes a significant minority of surgical site infections and nosocomial sinusitis cases as well as occasional cases of osteomyelitis contiguous to soft tissue infection, temperate myositis, and neonatal meningitis or meningitis associated with neurosurgery.

*Bacteremia Klebsiella* infection at any site can result in bacteremia. Infections of the urinary tract, respiratory tract, and abdomen each account for 15 to 30% of *Klebsiella* bacteremias. Intravascular device-related infection is another important source (5 to 15%). Surgical site infection and other miscellaneous infections account for the rest. *Klebsiella* is one of the agents that causes sepsis neonatorum and bacteremia with fever and neutropenia. Like entericGNB in general, *Klebsiella* rarely causes endocarditis or endovascular infection.

**Diagnosis** Except for *K. rhinoscleromatis* and *K. ozaenae*, klebsiellae are readily isolated and identified by the laboratory and usually ferment lactose.

## TREATMENT

*K. pneumoniae* and *K. oxytoca* have similar antibiotic resistance profiles. They are intrinsically resistant to ampicillin and ticarcillin.NNISdata from 1998 indicated that 10.7% ofICUpatients were infected with strains resistant to third-generation cephalosporins. This increasing degree of resistance is primarily mediated by transferable plasmids containing genes that encodeESBLs. In addition, these plasmids usually possess linked resistance determinants for aminoglycosides, tetracyclines, andTMP-SMZ. Resistance tob-lactam/b-lactamase inhibitor combinations and second-generation cephalosporins independent of ESBL-containing plasmids has also been increasingly described. In some outbreaks, ESBL-containing strains have displayed associated fluoroquinolone resistance. At this time, resistance to quinolones, cephamycins (e.g., cefoxitin), fourth-generation cephalosporins (e.g., cefepime), and amikacin is generally <10% but will probably increase. Carbapenems (e.g., imipenem) remain the most active antibiotic class against *Klebsiella*.

## *PROTEUS* INFECTIONS

*P. mirabilis* causes 90% of *Proteus* infections. These infections occur in the community, in long-term-care facilities, and in hospitals. *P. vulgaris* and *P. penneri* are isolated primarily from infections contracted in long-term-care facilities or hospitals. *Proteus* species are part of the colonic flora of a wide variety of mammals, birds, fish, and reptiles. Their ability to generate histamine from contaminated fish has implicated theseGNB in the pathogenesis of scombroid (fish) poisoning (Chap. 131). *P. mirabilis* colonizes healthy humans (prevalence, 50%), but *P. vulgaris* and *P. penneri* are isolated

primarily from individuals with underlying disease. The urinary tract is overwhelmingly the favored site of *Proteus* infection, in part because of unique pathogenic properties of the organisms. However, *Proteus* less commonly causes infection in a variety of extraintestinal sites.

**Infectious Syndromes**

*UTIP. mirabilis* causes only 1 to 2% of cases ofUTI in healthy women, and *Proteus* species cause only 5% of cases of hospital-acquired UTI. However, *Proteus* is responsible for 10 to 15% of cases of complicated UTI, primarily those associated with catheterization; in the setting of long-term catheterization, their prevalence rate ranges from 20 to 45%. This high prevalence is due to the ability of *Proteus* to produce high levels of urease, which hydrolyzes urea to ammonia and results in alkalization of the urine. This situation, in turn, leads to precipitation of organic and inorganic compounds, with the formation of struvite and carbonate-apatite crystals, biofilm formation on catheters, and/or the development of calculi. *Proteus* becomes associated with the stones and usually can be eradicated only by complete stone removal. Over time, staghorn calculi may form and lead to obstruction and renal failure. Therefore, an unexplained alkaline urine should be cultured for *Proteus*, and identification of a *Proteus* species should prompt an evaluation for calculi.

*Other Infections* Although the majority of *Proteus* infections arise from the urinary tract, these bacteria occasionally cause pneumonia (primarily in long-term-care or hospitalized patients), nosocomial sinusitis, intraabdominal abscesses, biliary tract infection, surgical site infection, soft tissue infection (especially decubitus and diabetic ulcers), and osteomyelitis (primarily contiguous); they rarely cause temperate myositis. In addition, *Proteus* occasionally causes neonatal meningitis (with the umbilicus often implicated as the source), and cerebral abscess is a common complication.

*Bacteremia* The majority of *Proteus* bacteremias originate from the urinary tract; however, any of the less common sites of infection are also potential sources. Infection of intravascular devices should also be considered. Endovascular infection is rare. *Proteus* species are occasional agents of sepsis neonatorum and bacteremia with fever and neutropenia.

**Diagnosis** *Proteus* is readily isolated and identified by the laboratory. The majority of strains are lactose negative, and most demonstrate characteristic "swarming" motility on agar plates.

**TREATMENT**

*P. mirabilis* remains susceptible to most antimicrobial agents except tetracycline. Resistance to ampicillin and first-generation cephalosporins has been acquired by 10 to 20% of strains. Acquisition ofESBLsremains uncommon. *P. vulgaris* and *P. penneri* are more resistant. Resistance to ampicillin and first-generation cephalosporins is the rule for these species. Derepression of an inducible chromosomalb-lactamase (not present in *P. mirabilis*) occurs in up to 30% of strains. Imipenem, fourth-generation cephalosporins (e.g., cefepime), aminoglycosides,TMP-SMZ, and quinolones have excellent activity (90 to 100%).

## *ENTEROBACTER* INFECTIONS

*E. cloacae* and *E. aerogenes* are responsible for most *Enterobacter* infections (65 to 75% and 15 to 25%, respectively); *E. agglomerans*, *E. sakazakii*, and *E. gergoviae* are less commonly isolated (5%, 1%, and<1%, respectively). These organisms cause primarily health care- or hospital-related infections. They are prevalent in foods, environmental sources (including health care facility equipment), and a wide variety of animals. Only a minority of healthy humans are colonized, but the percentage increases significantly in the setting of long-term care or hospitalization. Although colonization is an important prelude to infection, direct introduction via intravenous lines (e.g., contaminated intravenous fluids, pressure monitors) also occurs. Significant antibiotic resistance has developed in *Enterobacter* species and has contributed to their emergence as prominent nosocomial pathogens. Individuals who have received prior antibiotic treatment, who have comorbid disease, and who are patients inICUs are at greatest risk for infection. *Enterobacter* causes a spectrum of extraintestinal infections similar to that described for otherGNB in this chapter.

**Infectious Syndromes** Pneumonitis,UTI(particularly catheter-related), intravascular device-related infection, surgical wound/site infection, and abdominal infection (primarily postoperative or device-related -- e.g., biliary stents) are the most common syndromes encountered. Nosocomial sinusitis, meningitis related to neurosurgical procedures (including use of pressure monitors), osteomyelitis, and endophthalmitis after eye surgery are less frequent. *E. sakazakii* is commonly responsible for neonatal meningitis/sepsis (particularly in premature infants), and contaminated formula has been implicated as a source of this infection. Neonatal meningitis is frequently associated with brain abscesses. Bacteremia can result from infection at any of these sites. In the setting of *Enterobacter* bacteremia, contamination of intravenous fluids, blood products, catheter-flushing fluids, pressure monitors, and dialysis equipment should always be considered, particularly with epidemic infection. *Enterobacter* can also cause bacteremia in patients with fever and neutropenia. *Enterobacter* endocarditis is rare, primarily affecting abnormal native or prosthetic valves.

**Diagnosis** *Enterobacter* is readily isolated and identified by the laboratory. Most strains are lactose positive.

## TREATMENT

Significant antimicrobial resistance exists among *Enterobacter* strains. Ampicillin and the first- and second-generation cephalosporins have little or no activity. The extensive use of third-generation cephalosporins has resulted in the selection of strains that produce high levels ofb-lactamase (i.e., derepression ofb-lactamase), which confers resistance to second- and third-generation cephalosporins, monobactams (e.g., aztreonam), and (frequently)b-lactam/b-lactamase inhibitor combinations. Resistant isolates may emerge during therapy; their presence should be considered a possibility when clinical deterioration follows several days of improvement. A 34% resistance rate to third-generation cephalosporins was reported inICUisolates in 1998 (NNISdata). Imipenem, fourth-generation cephalosporins (e.g., cefepime), aminoglycosides (amikacin > gentamicin),TMP-SMZ, and quinolones have retained excellent activity (90

to 99%). However, increasing resistance to quinolones, in conjunction with the increased use of these agents, is a concern.

## *ACINETOBACTER* INFECTIONS

*A. baumannii* is responsible for the majority of *Acinetobacter* infections; a minority are due to *A. calcoaceticus* and *Acinetobacter* genospecies 3 and 13TU. *Acinetobacter* is highly prevalent in the environment. It is found in most water and soil samples and has a wide habitat. *Acinetobacter* has been cultured from the moist skin of healthy humans; increased colonization of the skin and the respiratory and gastrointestinal tracts occurs in individuals in long-term-care facilities and hospitals. Reservoirs for acquisition in these settings include health care personnel, medical equipment, food, and the surrounding environment. Infections in healthy people in the community are unusual, but a few reports of pneumonia have been published. The overwhelming majority of infections are acquired in the hospital and long-term-care facilities. The spectrum of extraintestinal infections caused by *Acinetobacter* is similar to that caused by otherGNB. *Acinetobacter* species account for 1 to 3% of hospital-acquired infections and affect primarily immunocompromised hosts and patients with comorbid disease.ICUs are a prominent site of *Acinetobacter* infection. In some centers, the incidence of *Acinetobacter* infections, particularly those due to antibiotic-resistant strains, is increasing. Both sporadic and epidemic infection occurs, usually after the first week of hospitalization.

**Infectious Syndromes** The respiratory tract (particularly in ventilated patients) and intravascular devices (particularly for non-*A. baumannii* species) are the favored sites of infection. A catheterized urinary tract, postoperative sites, burn sites, biliary stents, sinuses (with tube-related ostial obstruction), and neurosurgical infections (site- or device-associated -- e.g., pressure monitors) are less common. Uncommon infections include contiguous osteomyelitis, peritonitis associated with continuous ambulatory peritoneal dialysis, and ophthalmic infection. The respiratory tract and intravascular devices are the most common sources for bacteremia.

**Diagnosis** On Gram's stain, *Acinetobacter* organisms usually appear as shortGNB or coccobacilli. They are strictly aerobic, nonfermenting, and readily isolated and identified.

## TREATMENT

Many strains of *Acinetobacter* are highly resistant to antimicrobial agents. Empirical combination therapy is prudent pending susceptibility studies. Ampicillin, aztreonam, and the first- and second-generation cephalosporins possess little or no activity against these species. The activity of mezlocillin, piperacillin, quinolones, third- and fourth-generation cephalosporins, aminoglycosides, andb-lactam/b-lactamase inhibitor combinations is variable. Imipenem is presently the most active antimicrobial (>95% sensitivity), andb-lactam/sulbactam combinations are often active. Amikacin, third- and fourth-generation cephalosporins, quinolones, and combinations consisting of a b-lactam other than sulbactam plus a b-lactamase inhibitor retain significant activity in some centers, while highly resistant strains are more common in other centers.

## *SERRATIA* INFECTIONS

*S. marcescens* causes the majority of *Serratia* infections (>90%), and *S. liquefaciens* is occasionally isolated. Serratiae are found primarily in the environment, including health care institutions and particularly in moist foci. Although strains have been isolated from a variety of animals, healthy humans are rarely colonized. In long-term-care facilities or hospitals, diverse reservoirs for the organisms include the hands of health care personnel, food, sinks, respiratory and other hospital equipment, intravenous solutions, blood products (e.g., platelets), lotions, irrigation solutions, and even disinfectants. Infection results from either direct inoculation (e.g., via intravenous fluid) or colonization (primarily of the respiratory tract) and subsequent infection. Sporadic infection is most common, but occasional epidemics and common-source outbreaks occur. The spectrum of extraintestinal infections caused by *Serratia* is similar to that for otherGNB. *Serratia* species account for 1 to 3% of hospital-acquired infections.

**Infectious Syndromes** The respiratory tract, the genitourinary tract, intravascular devices, and surgical wounds and sites are the most common sites of *Serratia* infection and sources of *Serratia* bacteremia. Soft tissue infections, including myositis, osteomyelitis, abdominal and biliary tract infection (postprocedural), contact lens-associated infection, endophthalmitis, septic arthritis (primarily with intraarticular injections), and infusion-related bacteremias occur less commonly. Serratiae are uncommon causes of neonatal or postsurgical meningitis and bacteremia associated with fever and neutropenia. Endocarditis is rare.

**Diagnosis** Serratiae are readily cultured and identified by the laboratory and are usually lactose negative. A minority of *S. marcescens* strains are red-pigmented.

## TREATMENT

A high proportion of *Serratia* strains (>80%) are resistant to ampicillin and the first-generation cephalosporins. Significant resistance to ticarcillin, piperacillin, gentamicin, second- and third-generation cephalosporins,b-lactam/b-lactamase inhibitor combinations, and aztreonam has developed and may evolve during therapy. Imipenem, amikacin, cefepime, and quinolones are the most active agents, with >90% of strains susceptible.

## *CITROBACTER* INFECTIONS

*C. freundii* and *C. koseri* (formerly *C. diversus*) cause the majority of human *Citrobacter* infections, which are similar epidemiologically and clinically to *Enterobacter* and *Acinetobacter* infections. *Citrobacter* organisms are commonly present in water, food, soil, and the intestinal tracts of animals. *Citrobacter* is part of the normal fecal flora in a minority of healthy humans, but colonization rates increase in long-term care facilities and hospitals -- the settings in which nearly all infections occur. *Citrobacter* species account for 1 to 2% of nosocomial infections. The affected hosts are usually immunocompromised or have comorbid disease. *Citrobacter* causes extraintestinal infections whose spectrum is similar to that described for otherGNB.

**Infectious Syndromes** The urinary tract is the site of 40 to 50% of infections due to *Citrobacter*. Less commonly infected sites include the biliary tree (particularly with

stones or obstruction), the respiratory tract, surgical sites, soft tissue (e.g., decubitus ulcers), the peritoneum, and intravascular devices. Osteomyelitis (usually contiguous), neurosurgery-related infection, and myositis occur rarely. *Citrobacter* is also an uncommon cause of neonatal meningitis; *C. koseri* accounts for 90% of cases due to this genus. A frequent and devastating complication of this infection (occurring in 50 to 80% of cases) is the development of brain abscesses. Bacteremia is most commonly due to UTI, biliary or abdominal infection, or intravascular devices. *Citrobacter* is an uncommon cause of bacteremia in the setting of fever and neutropenia. Endocarditis or endovascular infection is rare.

**Diagnosis** *Citrobacter* species are readily isolated and identified, often as part of a polymicrobial culture; 35 to 50% of isolates are lactose positive.

## TREATMENT

*C. freundii* is generally more resistant to antibiotics than *C. koseri*. Ampicillin and the first- and second-generation cephalosporins display poor activity against *Citrobacter*. Resistance is variable but increasing to ticarcillin, mezlocillin, piperacillin, aztreonam, quinolones, gentamicin, and third-generation cephalosporins; such resistance may evolve during therapy. Theb-lactamase inhibitors usually do not improve susceptibility to b-lactam agents. Imipenem, amikacin, and the fourth-generation cephalosporins are most active, with>90% of strains sensitive.

## *MORGANELLA* AND *PROVIDENCIA* INFECTIONS

*M. morganii* (formerly *Proteus morganii*), *P. stuartii*, and (to a lesser degree) *P. rettgeri* (formerly *Proteus rettgeri*) are the members of these genera that are responsible for human infections. The epidemiologic, pathogenic, and clinical manifestations of these organisms are similar to those of *Proteus* species; however, *Morganella* and *Providencia* are almost exclusively pathogens of persons in long-term-care facilities and, to a lesser degree, hospitalized patients.

**Infectious Syndromes** These species are primarily urinary tract pathogens, most often associated with long-term (>30-day) catheterization.UTI in uncatheterized or short-term-catheterized individuals is uncommon. Biofilm formation or encrustation of the catheter usually develops and may lead to catheter obstruction. Likewise, infection may result in the development of struvite bladder or renal stones, which, in turn, may lead to renal obstruction and serve as foci for relapse. Other infectious syndromes occur less commonly but include surgical wound/site infections, soft tissue infection (primarily decubitus and diabetic ulcers), burn site infection, pneumonia (particularly ventilator-associated), intravascular device infection, and intraabdominal infection. Rarely, the other extraintestinal infections described forGNB also occur. Bacteremia is uncommon; although any infected site can serve as the source, the urinary tract accounts for the majority of cases, with surgical wound/site and soft tissue infections less frequently responsible.

**Diagnosis** *M. morganii* and *Providencia* are readily isolated and identified. Nearly all isolates are unable to ferment lactose.

## TREATMENT

*Morganella* and *Providencia* may be highly resistant to antimicrobial agents. Ampicillin and the first-generation cephalosporins exhibit poor activity against these organisms. Variable resistance is emerging (and may evolve during therapy) against ticarcillin, mezlocillin, piperacillin, aztreonam, gentamicin,TMP-SMZ, and the second- and third-generation cephalosporins and quinolones. Theb-lactamase inhibitor tazobactam (but not sulbactam or clavulanic acid) improves susceptibility to b-lactam agents somewhat. Imipenem, amikacin, and the fourth-generation cephalosporins are most active, with >90% of strains susceptible. Removal of an infected catheter or stones is critical for eradication of the organisms from the urinary tract.

## *EDWARDSIELLA* INFECTION

*E. tarda* is the only member of this genus associated with human disease. This organism is found predominantly in both freshwater and marine environments and in the animals that live in these environments. Human acquisition occurs primarily during interaction with these reservoirs. *E. tarda* infection is rare in the United States; most recently reported cases are from Southeast Asia. This pathogen shares some of the clinical features of both *Salmonella* species and *Vibrio vulnificus*.

**Infectious Syndromes** Gastroenteritis is the predominant infectious syndrome reported (50 to 80% of infections). Self-limiting watery diarrhea is most frequent; however, cases of severe colitis responding to therapy have also been described. The most common extraintestinal infection is wound infection due to direct inoculation, which is often associated with freshwater, marine, or snake-related injuries. Other infectious syndromes appear to be due to invasion of the gastrointestinal tract and subsequent bacteremia. The majority of afflicted hosts have either liver disease or an iron-overload state (e.g., sickle cell disease). A primary bacteremic syndrome, sometimes complicated by meningitis, has been described and has a 40% case-fatality rate. Visceral (primarily hepatic) or intraperitoneal abscesses have also been reported.

**Diagnosis** Although *E. tarda* can readily be isolated and identified, most laboratories do not routinely identify it from stool.

## TREATMENT

*E. tarda* is sensitive to mostGNB-appropriate antimicrobial agents. Gastroenteritis is generally self-limiting, but treatment withTMP-SMZor a quinolone may expedite its resolution. In the setting of overwhelming sepsis, quinolones, third- or fourth-generation cephalosporins, imipenem, and aminoglycosides -- alone or in combination -- are the safest choices pending susceptibility information.

## INFECTIONS CAUSED BY MISCELLANEOUS GENERA

Species from genera ofGNB such as *Hafnia*, *Kluyvera*, *Cedecea*, *Pantoea*, and *Ewingella* are occasionally isolated from a variety of clinical specimens, including blood, sputum, cerebrospinal fluid, joint fluid, biliary drainage, wounds, and sputum. Although their role in disease has not always been defined, these strains appear to be rare and

usually opportunistic human pathogens. The primary medical literature should be consulted for details on their potential role as infectious agents.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 154. *HELICOBACTER PYLORI* INFECTIONS - *John C. Atherton*, *Martin J. Blaser*

### DEFINITION

*Helicobacter pylori* colonizes the human stomach and is of etiologic importance in peptic ulcer disease and gastric malignancy. Other gastric *Helicobacter* species colonize animals, some with a narrow range and others with a broad range of host species specificity. Those with broad specificity are occasionally found in humans, possibly as zoonoses. It is unclear whether *Helicobacter heilmanii* (formerly known as *Gastrospirillum hominis*), the most common of these species among isolates from humans, is associated with human disease. Numerous species of nongastric helicobacters are found in animals, and some have been isolated from human stool and gall bladder; whether these species cause disease is unknown.

### ETIOLOGIC AGENT

*H. pylori* is a gram-negative, spiral, flagellate bacillus that naturally colonizes humans and monkeys. It is noninvasive, living in gastric mucus; a small proportion of the bacterial cells are adherent to the mucosa. Its spiral shape and flagellae render *H. pylori* motile in the mucous environment, and its efficient urease protects it against acid by catalyzing urea hydrolysis to produce buffering ammonia. In vitro, *H. pylori* is microaerophilic and slow-growing and requires complex growth media. In 1997, the complete genomic sequence of *H. pylori* was published, and this information has greatly advanced the understanding of metabolic pathways and other aspects of the organism's biology. *H. heilmanii* is a longer, more tightly coiled spiral than *H. pylori* and cannot easily be cultured in vitro at present.

### EPIDEMIOLOGY

The prevalence of *H. pylori* colonization is about 30% in the United States and other developed countries as opposed to >80% in most developing countries. In the United States, prevalence varies with age; around 50% of 60-year-old persons as opposed to 25% of 30-year-old persons are colonized. Spontaneous acquisition or loss of the bacterium in adulthood is uncommon. *H. pylori* is usually acquired in childhood. (The age association is mostly due to a birth-cohort effect.) Other than age, the main risk factor for colonization is low socioeconomic status; crowding and low family income in childhood are especially strong correlates of colonization.

Humans are the only important reservoir of *H. pylori*. Members of a family may carry the same strain, and colonization is particularly common in childhood institutions. These findings imply direct person-to-person spread, but whether transmission takes place by the fecal-oral or oral-oral route is unknown. *H. pylori* DNA has been found in water sources, and indirect epidemiological evidence indicates that contaminated water may lead to human colonization in developing countries. Much research is focused on determining which of these possible routes of acquisition is most important.

### CLINICAL MANIFESTATIONS

Essentially all *H. pylori*-colonized persons have gastric inflammation, but this condition

in itself is asymptomatic (Fig. 154-1). Symptoms are due to illnesses such as peptic ulceration or gastric malignancy, which develop in fewer than 10% of individuals colonized with *H. pylori*. More than 80% of peptic ulcers are related to *H. pylori* colonization, most of the remainder being due to damage caused by aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). The main lines of evidence for an ulcer-promoting role of *H. pylori* are (1) that the presence of the organism is a risk factor for the development of ulcers, (2) that (non-NSAID-induced) ulcers rarely develop in the absence of *H. pylori*, (3) that eradication of *H. pylori* results in a dramatic drop in the rate of ulcer relapse (from about 80% to 15% in the first year), and (4) that experimental infection of gerbils and mice causes gastroduodenal injury.

Prospective case-control studies have shown that *H. pylori* colonization is a risk factor for adenocarcinomas of the stomach (other than those arising in the gastric cardia). However, persons who have had documented duodenal ulcers are less likely than other persons to develop gastric adenocarcinoma later in life; the implication is that, whereas *H. pylori* colonization increases risk for both duodenal ulcerogenesis and gastric carcinogenesis, other factors determine which disease path is taken. The presence of *H. pylori* is strongly associated with gastric lymphoma. Low-grade B-cell mucosa-associated lymphoid tissue (MALT) lymphomas, which are antigen driven, often regress following *H. pylori* eradication. Whether all such diagnosed cases represent true malignancies remains to be determined.

Most *H. pylori* colonization is asymptomatic. Whether colonization occasionally causes symptoms (nonulcer dyspepsia) in the absence of ulcers or malignancy is controversial. Some but not all trials of *H. pylori* eradication in nonulcer dyspepsia have shown a reduction of symptoms in a small proportion of patients. As there is no prospective method for identifying this small group, eradication of *H. pylori* in patients with nonulcer dyspepsia is not currently indicated.

Much interest has focused on a possible protective role for *H. pylori* in gastroesophageal reflux disease (GERD) and adenocarcinoma of the esophagus and gastric cardia. The main lines of evidence for this role are that (1) there is a temporal relationship between a falling prevalence of *H. pylori* colonization and a rising incidence of these conditions; (2) in most studies, the prevalence of *H. pylori* colonization, especially with *cagA*$^+$strains, is lower among patients with these esophageal diseases than among control subjects; and (3) eradication of *H. pylori* often leads to the development or worsening of GERD or its symptoms. Although there are plausible mechanisms for a protective effect of *H. pylori* against these diseases, none has yet been definitively identified. Thus a causal link remains probable but unproven.

Several extra-gastrointestinal pathologies have been linked epidemiologically with *H. pylori* colonization. The most notable are ischemic heart disease and cerebrovascular disease. The associations have been found more commonly in small than in large studies, and most authorities consider them to be noncausal and due to confounding factors.

## PATHOLOGY AND PATHOGENESIS

*H. pylori* colonization induces chronic superficial gastritis, which includes both

mononuclear and polymorphonuclear cell infiltration of the mucosa. (The term *gastritis* should be used specifically to describe histologic features; it also has been used to describe endoscopic appearances and even symptoms, neither of which have been linked to microscopic findings or to the presence of *H. pylori*.) The immune response to *H. pylori* includes both the production of antibody (local and systemic) and a cell-mediated response but is ineffective in clearing the bacterium. *H. pylori* and associated inflammation are most evident in the stomach but are also found in areas of gastric metaplasia and heterotopia (e.g., the duodenal bulb).The pattern of gastric inflammation is associated with disease risk: antral-predominant gastritis is most closely linked with duodenal ulceration and is common in the United States and other developed countries, whereas the predominant form in developing countries is pangastritis, which is epidemiologically linked with gastric ulceration and adenocarcinoma. Longitudinal analyses of gastric biopsy specimens taken years apart from the same patient show that inflammation may progress to atrophy, intestinal metaplasia, and dysplasia and then (by implication) to carcinoma. Patients with atrophic gastritis are at risk for vitamin $B_{12}$deficiency and its associated hematologic and neurologic sequelae. Continuous omeprazole therapy (for example, forGERD) may speed progression to atrophy when *H. pylori* is present.

Most *H. pylori*-colonized persons do not develop clinical sequelae. That some persons develop overt disease whereas others do not is probably due to a combination of bacterial strain differences, host susceptibility to disease, and environmental factors; of these, bacterial factors are best studied.

The two major disease-associated *H. pylori* virulence factors described so far are a vacuolating cytotoxin, VacA, and a group of genes termed the *cag* pathogenicity island (*cag* PaI). VacA occurs in several forms, and its level of production varies between strains; thus, although all strains have the gene (*vacA*) encoding the protein, not all exhibit vacuolating activity in vitro. Cytotoxic strains are more commonly isolated from patients with peptic ulcer disease than from persons without ulcers. The *cag* PaI includes genes that confer enhanced virulence on *H. pylori* strains, at least partly by inducing epithelial cells to produce proinflammatory cytokines. The gene *cagA*, an imperfect marker for the *cag* PaI, is useful for epidemiologic studies because it encodes a highly immunogenic protein, CagA. Patients with peptic ulcers or gastric adenocarcinoma are more likely to have CagA antibodies than persons without these conditions. However, patients with esophageal dysplasia or adenocarcinoma or with the premalignant condition Barrett's esophagus are less likely to harbor *cagA*$^+$strains than are *H. pylori*-positive controls. Thus, eradication of *cagA*$^+$strains from asymptomatic persons to prevent disease is not recommended.

How does gastric *H. pylori* colonization increase risk for duodenal ulceration? One explanation is that antral *H. pylori* colonization diminishes the number of somatostatin-producing cells; somatostatin-mediated inhibition of gastrin release leads to hypergastrinemia. Individuals with antral-predominant gastritis (and thus a normally functioning acid-producing gastric corpus) develop increased acid secretion, which may increase the risk of duodenal ulceration per se or may induce gastric metaplasia in the duodenum, which becomes colonized by *H. pylori*, then inflamed, and finally ulcerated. After eradication of *H. pylori* from patients with duodenal ulcer disease, the level of acid secretion often falls.

## DIAGNOSIS

Tests for *H. pylori* can be divided into two groups: invasive tests, which require upper gastrointestinal endoscopy and are based on the analysis of gastric biopsy specimens, and noninvasive tests (Table 154-1). Invasive tests are preferred for (1) the initial management of dyspeptic patients, because the decision of whether or not to eradicate *H. pylori* depends on ulcer disease status, and (2) follow-up after treatment of patients with gastric ulceration to be certain that the ulcer was not malignant. Follow-up endoscopy should be performed at least 4 weeks after cessation of all anti-*Helicobacter* drugs, since at earlier points the *H. pylori* load may be low and tests may be falsely negative. The most convenient endoscopy-based test is the biopsy urease test, in which two antral biopsy specimens are put into a gel containing urea and an indicator. The presence of *H. pylori* urease elicits a color change, which often takes place within minutes but can require up to 24 h. Histologic examination of biopsy specimens is accurate, provided that a special stain (e.g., a modified Giemsa or silver stain) permitting optimal visualization of *H. pylori* is used. Histologic study yields additional information, including the degree and pattern of inflammation, atrophy, metaplasia, and dysplasia, although these details are rarely of clinical use. Microbiologic culture is most specific but may be insensitive due to difficulty with *H. pylori* isolation. Once cultured, the identity of *H. pylori* can be confirmed by its typical appearance on Gram's stain and its positive reactions in oxidase, catalase, and urease tests. Antibiotic sensitivities also can be determined. Specimens containing *H. heilmanii* are only weakly positive in the biopsy urease test. The diagnosis is based on visualization of the characteristic long, tight spiral bacteria in histologic sections.

The simplest tests for *H. pylori* infection are serologic, involving the assessment of specific IgG levels in serum. The best of these tests are as accurate as other diagnostic methods, but many commercial tests, especially rapid office tests, perform poorly. In quantitative tests, a defined drop in antibody titer between matched serum samples taken before and 6 months after treatment (no sooner because of the slow decline in antibody titer) accurately indicates that *H. pylori* infection has been eradicated. The other major noninvasive tests are the $^{13}C$ and $^{14}C$ urea breath tests. In these simple tests, the patient drinks a labeled urea solution and then blows into a tube. The urea is labeled with either the nonradioactive isotope $^{13}C$ or a minute dose of the radioactive isotope $^{14}C$ (which exposes the patient to less radiation than a standard chest x-ray). If *H. pylori* urease is present, the urea is hydrolyzed and labeled carbon dioxide is detected in breath samples. Unlike serologic tests, urea breath tests can be used to assess the outcome of treatment 1 month after its completion and thus may replace endoscopy for this purpose in the follow-up of duodenal ulcer patients. As for endoscopic tests, all anti-*Helicobacter* drugs should be avoided in this period or the test may be falsely negative.

## TREATMENT

At present, the only clear indications for treatment are *H. pylori*-related duodenal and gastric ulceration and the rare low-grade B-cell MALT lymphoma. *H. pylori* should be eradicated in patients with documented ulcer disease, whether or not the ulcers are currently active, to reduce the likelihood of relapse. At present, treatment is not

recommended for nonulcer dyspepsia or for prophylaxis against ulcers or gastric adenocarcinoma (although it may be reasonable to eradicate *H. pylori* in persons with a strong family history of gastric cancer). Reasons for avoiding treatment for these other potential indications include the expense, the induction of morbidity in otherwise healthy people, the risk of inducing widespread antibiotic resistance in *H. pylori* and in other colonizing bacteria, and the risk of inducing or worseningGERD.

*H. pylori* is susceptible to a wide range of antibiotics in vitro, but monotherapy has been disappointing in vivo, probably because of inadequate antibiotic delivery to the full locus of colonization. Failure of monotherapy has led to the development of multidrug regimens, the most successful of which are triple and quadruple combinations that achieve *H. pylori* eradication rates of >90% in many trials and>75% in clinical practice. Current 7- to 14-day drug regimens consisting of a proton pump inhibitor and two or three antimicrobial agents often require only twice-daily dosing (Table 154-2).

The two most important goals in *H. pylori* eradication are to obtain the patient's compliance with the dosing regimen and to use drugs to which *H. pylori* has not acquired resistance. Treatment failure following minor lapses in compliance is common and often leads to acquired resistance to metronidazole or clarithromycin. To stress the importance of compliance, written instructions should be given to the patient, and minor side effects of the regimen should be explained. Resistance to metronidazole and clarithromycin is of growing concern; however, in multidrug regimens, the clinical significance of single-drug resistance is diminished. Assessment of antibiotic susceptibilities before treatment would be optimal but is not usually undertaken. In the absence of susceptibility information, a history of antibiotic use should be obtained, and, if resistance is likely, metronidazole-containing regimens should be avoided. Metronidazole resistance is common among persons who have taken the agent previously, even years earlier, for other conditions such as giardiasis or trichomoniasis. If initial *H. pylori* treatment fails, compliance should be checked and re-treatment should be based on known antibiotic susceptibilities. When this information cannot be obtained, the recommended course is quadruple therapy without clarithromycin (if a clarithromycin-containing regimen was given first) or triple therapy with omeprazole/clarithromycin/amoxicillin (if clarithromycin has not been used) (Table 154-2).

Given the high efficacy of treatment regimens, it is unclear whether the success of attempted *H. pylori* eradication should be checked. For gastric ulceration, the opportunity to retest for *H. pylori* is present at the repeat endoscopy, which is performed to evaluate healing. For duodenal ulceration, although many clinicians prefer to retest only if symptoms recur, a urea breath test or endoscopy should be performed no sooner than 1 month after treatment. This test will provide reassurance if treatment has been successful and will prompt re-treatment in cases of persistence.

Clearance of *H. heilmanii* has been described following the use of bismuth compounds alone or triple-therapy regimens. However, in the absence of trials, it is unclear whether this result represents successful treatment or natural clearance of the bacterium.

**PREVENTION**

Carriage of *H. pylori* has public health significance in developing countries, where gastric adenocarcinoma is a common cause of cancer death. However, *H. pylori* has co-evolved with its human host over millennia, and there may be disadvantages in preventing or eliminating colonization. For example, as has been mentioned, the absence of *H. pylori* appears to increase the risk of developingGERD and esophageal adenocarcinoma. If mass prevention were contemplated, vaccination would be preferred, and experimental immunization of animals has given promising results. However, in the United States and other developed countries, the incidences of *H. pylori* carriage, peptic ulceration, and gastric adenocarcinoma are dropping. Thus, prevention of colonization in these countries may be unnecessary or even unwise.

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Back to Table of Contents

# 155. INFECTIONS DUE TO *PSEUDOMONAS* SPECIES AND RELATED ORGANISMS

***- Christopher A. Ohl*, *Matthew Pollack***

*Pseudomonas* species and phylogenetically related bacteria are ubiquitous, free-living, opportunistic gram-negative pathogens. *P. aeruginosa*, the most common human pathogen in this group, is the primary subject of this chapter. Also discussed are two pathogens of increasing importance: *Burkholderia cepacia* (formerly *P. cepacia*), primarily an opportunistic pathogen, and *Stenotrophomonas maltophilia* (formerly *Xanthomonas maltophilia*), which principally infects hospitalized patients. In addition, melioidosis, a tropical systemic disease with acute and chronic manifestations caused by *B. pseudomallei* (formerly *P. pseudomallei*), will be considered.

## INFECTIONS DUE TO *P. AERUGINOSA*

*P. aeruginosa* is a small, nonsporulating, aerobic gram-negative rod belonging to the family Pseudomonadaceae. It is motile by virtue of its single polar flagellum. More than half of all clinical isolates produce the blue-green pigment pyocyanin; this pigment is helpful in the identification of the organism and accounts for the species name *aeruginosa*, which refers to the distinctive color of copper oxide.

### EPIDEMIOLOGY

*P. aeruginosa* is widespread in nature, inhabiting soil, water, plants, and animals (including humans). It has a predilection for moist environments. This organism occasionally colonizes the skin, external ear, upper respiratory tract, or large bowel of healthy humans. Rates of carriage are relatively low, however, except among patients who have serious underlying disease, whose host defenses have been naturally or iatrogenically compromised, who have previously received antibiotic therapy, and/or who have been exposed to the hospital environment. Under these circumstances, colonization with *P. aeruginosa* frequently precedes infection, and factors that predispose to the former also increase the likelihood of the latter.

Most *P. aeruginosa* infections are acquired in the hospital, where intensive care units account for the highest rates of infection. According to the National Nosocomial Infections Surveillance (NNIS) system, between 1992 and 1999, *P. aeruginosa* was the second most common cause of pneumonia, the fourth most common cause of urinary tract infection, and the sixth most frequent bloodstream isolate in intensive care units. Many potential reservoirs of infection have been identified in the hospital environment, including respiratory equipment, cleaning solutions, disinfectants, sinks, vegetables, flowers, endoscopes, and physiotherapy pools. Most reservoirs are associated with moisture. It is assumed that the organism is transmitted to patients via the hands of hospital personnel or via fomites. While some infecting strains of *P. aeruginosa* appear to be endemic within the hospital, others are traced to a common source associated with a specific outbreak or epidemic. Epidemiologic investigation is facilitated by serotyping (immunotyping) of strains on the basis of differences in lipopolysaccharide (LPS) structure and by the use of molecular techniques such as pulsed-field gel electrophoresis.

### PATHOGENESIS

That the pathogenesis of infections due to *P. aeruginosa* is complex is evidenced by the clinical diversity of the diseases related to this organism and by the multiplicity of virulence factors it produces. *P. aeruginosa* rarely causes disease in the healthy host. Relative risk for infection is greatly increased, however, when normal cutaneous or mucosal barriers have been breached or bypassed, when immunologic defense mechanisms have been compromised, or when the protective function of the normal bacterial flora has been disrupted (Table 155-1). The ubiquity of the organism, its flexible nutritional and metabolic requirements, its environmental resiliency, and its relative resistance to antibiotics help account for the frequency and success with which it acts as an opportunistic pathogen.

Infections caused by *P. aeruginosa* usually begin with bacterial attachment and superficial colonization of cutaneous or mucosal surfaces and progress to localized bacterial invasion and damage to underlying tissues. The infection may remain anatomically localized or may spread by direct extension to contiguous structures. This process may continue with bloodstream invasion, dissemination, the systemic inflammatory-response syndrome (SIRS), multiple-organ dysfunction, and ultimately death. Not only is local infection more likely to occur in immunocompromised hosts, such as those with profound neutropenia, but it is more likely to culminate in bloodstream invasion and dissemination.LPS(endotoxin), which is a structural component of the bacterial outer membrane, is thought to play a pivotal role in the pathogenesis of the sepsis syndrome or SIRS.

The initial attachment of *P. aeruginosa* to the respiratory epithelium and other epithelial surfaces appears to be mediated by bacterial organelles called *pili* or *fimbriae* and facilitated by *alginate*, a mucoid exopolysaccharide produced by most strains of the bacterium under appropriate environmental conditions. Alginate plays an important role in colonization and infection of the respiratory tract in patients with cystic fibrosis and in the formation of biofilms within which sessile colonies of *P. aeruginosa* enjoy relative protection from host defenses and antimicrobial agents.

*P. aeruginosa* produces a number of extracellular virulence factors, including alkaline protease, elastase, phospholipase, cytotoxin, and exoenzymes (or exotoxins) A and S. The breakdown of host tissues by these bacterial products creates conditions conducive to enhanced bacterial proliferation, invasion, and tissue injury. Production and secretion of many of these extracellular virulence factors are under the regulatory control of a cell-to-cell signaling system that has been termed *quorum sensing*. Through lactones and other signal molecules secreted by individual *P. aeruginosa* bacteria, the entire bacterial population is able to sense its environment, communicate, and discern its own cell density. This regulatory system conceivably allows *P. aeruginosa* to produce extracellular virulence factors in a coordinated manner dependent on cell density and may give the pathogen an appreciable advantage over host defense mechanisms.

The extracellular enzyme exotoxin A -- a diphtheria-like toxin -- is produced by most clinical isolates of *P. aeruginosa*. Exotoxin A inhibits mammalian protein synthesis by transferring the adenosine diphosphate (ADP) ribose moiety of the nicotinamide adenine dinucleotide into covalent linkage with elongation factor 2, inactivating this factor's ability to catalyze the elongation step in polypeptide assembly. Another

extracellular cytotoxin, exoenzyme S, is also an adenosine diphosphate ribosyltransferase but, unlike exotoxin A, preferentially ribosylates guanosine triphosphate-binding proteins, resulting in disruption of host cell actin cytoskeletons. Exoenzyme S is one of several extracellular virulence factors of *P. aeruginosa* that is directly introduced from the bacterial cytosol into the host cell cytoplasm via a complex array of transmembrane proteins termed the *type III secretion apparatus*. This process requires direct cell contact and allows the injection of virulence factors from the bacterium into host cells without interference from humoral immune defenses.

## CLINICAL MANIFESTATIONS AND DIAGNOSIS

**Respiratory Tract Infections** *Primary pneumonia*, or *nonbacteremic pneumonia*, results from aspiration of upper respiratory tract secretions; often develops in patients with chronic lung disease, congestive heart failure, or AIDS; and is most common in an intensive care setting in association with mechanical ventilator use. Fever, chills, severe dyspnea, cyanosis, productive cough, apprehension, confusion, and other signs of severe systemic toxicity characterize this acute, often life-threatening infection. Chest roentgenograms typically show bilateral bronchopneumonia with nodular infiltrates and small areas of radiolucency; pleural effusions are common; empyema is relatively uncommon; and lobar consolidation is occasionally seen. Cavitary lesions are particularly common in AIDS patients with *P. aeruginosa* pneumonia. Pathologic lesions include alveolar necrosis, focal hemorrhages, and microabscesses.

*Bacteremic pneumonia* due to *P. aeruginosa* begins as a respiratory infection but, in contrast to primary pneumonia, is typically associated with neutropenia, subsequent bloodstream invasion, and metastatic spread that produces characteristic lesions in the lungs and other viscera. Alveolar hemorrhage and necrosis are common. The signs and symptoms of this fulminant disease include those described for nonbacteremic pneumonia caused by this organism as well as those associated with gram-negative sepsis. Chest roentgenograms characteristically demonstrate a rapid progression from pulmonary vascular congestion to interstitial edema, then to pulmonary edema, and finally to diffuse necrotizing bronchopneumonia with cavity formation. The patient typically dies 3 or 4 days after initial presentation.

Chronic infection of the lower respiratory tract with *P. aeruginosa* is caused almost exclusively by mucoid strains, which produce alginate. Such infection is prevalent among older children and young adults with cystic fibrosis and also develops in some patients with AIDS. In patients with cystic fibrosis, mucoid strains invariably colonize and infect patients with increasing prevalence over time, contributing to the acute exacerbations and chronic progression that characterize pulmonary disease in these individuals. Airway obstruction appears to begin with bronchiolitis, which causes mucus plugging and predisposes to *P. aeruginosa* infection. The infection produces more mucus plugging, chronic suppuration, bronchiectasis, atelectasis, and ultimately fibrosis. This process progresses to pulmonary insufficiency, hypoxemia, and alterations in cardiopulmonary dynamics resulting in pulmonary hypertension and cor pulmonale.

Clinical manifestations of lower respiratory tract infections due to *P. aeruginosa* in patients with cystic fibrosis vary with the severity and duration of underlying lung disease, the frequency and intensity of acute episodes, and the presence of coinfecting

pathogens such as *B. cepacia* (Chap. 257). Soon after colonization, patients may experience recurrent upper respiratory symptoms followed by a lingering cough. Episodes of pneumonia develop later, with persistent cough between acute episodes. Eventually, patients exhibit a chronic productive cough, wheezing, diminished appetite, weight loss, growth retardation, and decreased activity. Acute exacerbations are typically accompanied by low-grade fever and heightened respiratory symptoms. Physical signs include evidence of malnutrition, an increase in anteroposterior diameter, intercostal retractions, cyanosis, inspiratory and expiratory wheezing, rhonchi, moist rales, abdominal distention, and clubbing of the fingers and toes. Laboratory abnormalities include leukocytosis with a left shift and hypoxemia with or without hypercarbia. Tests of pulmonary function demonstrate obstructive and restrictive defects. Chest roentgenograms reveal overaeration, patchy atelectasis, peribronchial fibrosis, and patchy infiltrates associated with pneumonia. In more advanced disease, there may be evidence of severe overaeration, depressed diaphragm, further increased anteroposterior diameter, extensive peribronchial infiltration, generalized bronchiectasis, and cyst formation.

**Bacteremia** *P. aeruginosa* remains an important cause of life-threatening bloodstream infection in immunocompromised patients. Bacteremia is frequently iatrogenic and is usually seen in hospitalized patients with various comorbid conditions (Table 155-1). Bloodstream infection can be either primary (with no identifiable source) or secondary to a discrete focus of infection.

The clinical features of *P. aeruginosa* bacteremia are similar to those of other forms of bacteremia. Common primary sites of infection include the urinary tract, gastrointestinal tract, lungs, skin and soft tissues, and intravascular foci, including indwelling central venous catheters. Fever, tachypnea, tachycardia, and prostration are common. Disorientation, confusion, or obtundation may be evident. Hypotension can progress to refractory shock. Renal failure, adult respiratory distress syndrome, and disseminated intravascular coagulation occur as complications.

Pathognomonic skin lesions termed *ecthyma gangrenosum* (Fig. 19-CD1) develop in a relatively small minority of patients with *P. aeruginosa* bacteremia. The lesions begin as small hemorrhagic vesicles surrounded by a rim of erythema and undergo central necrosis with subsequent ulceration (seePlate IID-57C). They occur singly or in small numbers on the perineum, buttocks, and extremities; in the axillae; or elsewhere. Histologically, these lesions contain numerous bacteria invading blood vessels but few inflammatory cells. Bacteria are readily visible on Gram's staining and may be cultured from aspirated material.

**Endocarditis** *P. aeruginosa* infects native heart valves in injection drug users as well as prosthetic heart valves. The source of *P. aeruginosa* strains infecting drug users appears to be standing water contaminating drug paraphernalia. Foreign materials mixed with heroin may cause injury to valve leaflets or mural endocardium, with resulting fibrosis and an increased risk for valve infection. Exposure of the tricuspid valve to both trauma and bacteria apparently accounts for the high incidence of tricuspid involvement in association with injection drug use.

The pulmonic, mitral, or aortic valve and the mural endocardium of either atrium may be

affected in *P. aeruginosa* endocarditis. Multiple-valve infections are common. Tricuspid or right-sided involvement is often associated with septic pulmonary emboli. Right-sided *P. aeruginosa* endocarditis usually presents subacutely, while the appearance of left-sided disease is likely to be more acute or even fulminant. Fever is virtually invariable, and murmurs are usually detectable at initial presentation or shortly thereafter. Septic pulmonary emboli associated with right-sided disease result in cough, pleuritic chest pain, sputum production, pulmonary infiltration (with or without abscess formation), and pleural effusion. Left-sided infections may present as intractable heart failure or large systemic emboli. Mycotic aneurysms, cerebritis, or brain abscess may occur; septic infarcts are occasionally found in the spleen. Skin and soft tissue manifestations, including Janeway lesions, Osler's nodes, and ecthyma gangrenosum, are relatively uncommon.

The diagnosis of *P. aeruginosa* endocarditis is based on positive blood culture in the absence of an extracardiac source; an indication of valvular dysfunction or vegetation on an echocardiogram; evidence of septic pulmonary lesions on a chest roentgenogram (in right-sided disease); and the actual demonstration of infected heart valves at the time of surgery.

**Central Nervous System Infections** *P. aeruginosa* infections of the central nervous system include meningitis and brain abscess. These infections follow extension from a contiguous parameningeal structure such as the ear, mastoid, or paranasal sinus; direct inoculation into the subarachnoid space or brain through head trauma, surgery, or diagnostic procedures; or bacteremic spread from infection at a distant site. Like *P. aeruginosa* infections at other anatomic sites, central nervous system infections are documented almost exclusively in patients with compromised local or systemic immune-defense mechanisms.

The clinical signs of *P. aeruginosa* meningitis, like those of other forms of acute bacterial meningitis, include fever, headache, stiff neck, confusion, and obtundation. The onset of illness may be acute or even fulminant, particularly in bacteremic patients, with a precipitous downhill course, shock, coma, and early death. In nonbacteremic patients, *P. aeruginosa* meningitis or brain abscess may present more insidiously, with a paucity of systemic symptoms. This presentation is especially common in infections resulting from recent neurosurgery, cancer of the head and neck, or direct extension from a parameningeal focus of chronic infection. Occasionally, *P. aeruginosa* meningitis runs a subacute or relapsing course that is thought to be related to the intermittent release of bacteria from a loculated site of infection.

**Ear Infections** *P. aeruginosa* is often found in the external auditory canal, particularly under moist conditions and in the presence of inflammation or maceration (as in "swimmer's ear"). Moreover, this organism is the predominant pathogen associated with external otitis, a usually benign inflammatory process affecting the external auditory canal. The ear is painful or merely itchy, there is a purulent discharge, and pain is elicited by pulling on the pinna. The external canal appears edematous and is filled with detritus that often prevents visualization of the tympanic membrane.

*P. aeruginosa* occasionally penetrates the epithelium overlying the floor of the external auditory canal at the junction between bone and cartilage and invades underlying soft

tissue. The ensuing invasive process, which involves soft tissue, cartilage, and cortical bone, is typically slow but destructive. Termed *malignant external otitis*, this condition occurs predominantly in elderly diabetic patients but is reported occasionally in infants with other underlying diseases and rarely in elderly nondiabetic patients. Virtually all cases of malignant external otitis are caused by *P. aeruginosa*. From the external ear, the infection advances to the retromandibular area or parotid space and enters the mastoid air cells and temporal bone. Advancing osteomyelitis at the base of the skull often involves the seventh, ninth, tenth, and eleventh cranial nerves. The cavernous sinus can become involved, as can the contralateral petrous apex. The middle ear is commonly spared; meningitis and brain abscess are relatively rare complications.

Otorrhea and severe otalgia are common presenting symptoms of malignant external otitis. Facial-nerve paralysis tends to occur early, while other cranial-nerve palsies appear later. There may be a loss of hearing. Constitutional symptoms such as fever and weight loss are relatively uncommon. Physical examination almost always reveals remarkable tenderness of the pinna of the ear and abnormalities of the external auditory canal, including swelling, erythema, purulent discharge, debris, and granulation tissue in the canal wall. The tympanic membrane is often hidden from view and is sometimes perforated. Inflammation may involve the pinna as well as the periauricular, retromandibular, and mastoid areas.

Peripheral leukocytosis is relatively infrequent in malignant external otitis, while the erythrocyte sedimentation rate is usually markedly elevated. Cerebrospinal fluid occasionally exhibits pleocytosis and an elevation in the protein level. Computed tomography (CT) or magnetic resonance imaging (MRI) of the mastoid or temporal bone typically reveals bony erosions and new bone formation, while the floor of the skull may have soft tissue densities associated with areas of cellulitis. In addition, technetium 99m bone scans and gallium 67 scans frequently give positive results. Cultures of samples from the external auditory canal and of surgical specimens are almost always positive for *P. aeruginosa*.

**Eye Infections (See alsoChap. 28)** *P. aeruginosa* causes bacterial keratitis or corneal ulcer and endophthalmitis in the human eye. Keratitis due to *P. aeruginosa* may result from even minor corneal injury, which interrupts the integrity of the superficial epithelial surface and permits bacterial access to the underlying stroma. Corneal ulcer may complicate contact lens use, particularly when extended-wear soft contact lenses are involved. Contact lens solutions or the lenses themselves may be the source of the organism, which is probably inoculated into the eye at sites of minor lens-induced corneal damage. Patients who have sustained serious burns, have undergone ocular irradiation or tracheostomy, have been exposed to the intensive care environment, and/or are in a coma are also susceptible to *P. aeruginosa*-associated corneal ulcers. *P. aeruginosa* keratitis usually starts as a small central ulcer; spreads concentrically to involve a large portion of the cornea, sclera, and underlying stroma; and in some cases progresses to posterior corneal perforation.

The clinical manifestations of *P. aeruginosa* keratitis include a rapidly expanding, necrotic stromal infiltrate in the bed of an epithelial injury; surrounding epithelial edema; an anterior chamber reaction; and mucopurulent discharge adherent to the ulcer's surface. Corneal ulcer due to *P. aeruginosa* may advance rapidly to involve the entire

cornea in £2 days or may evolve subacutely over several days. Systemic symptoms are uncommon. Complications include corneal perforation, anterior chamber involvement, and endophthalmitis.

*P. aeruginosa* endophthalmitis is typically a rapidly progressive, sight-threatening condition that demands immediate therapeutic intervention. It may complicate penetrating injuries of the eye, intraocular surgery, hematogenous spread from other sites of *Pseudomonas* infection, or posterior perforation of corneal ulcers. Clinical manifestations may include eye pain, conjunctival hyperemia, chemosis, lid edema, decreased visual acuity, hypopyon, severe anterior uveitis, and signs of possible vitreous involvement. Panophthalmitis may result from this intraocular infection.

**Bone and Joint Infections** Vertebral osteomyelitis due to *P. aeruginosa* is associated with complicated urinary tract infection, genitourinary instrumentation or surgery, and injection drug use. Vertebral infections that are associated with a urinary tract source most often develop in the elderly and usually affect the lumbosacral spine. Presumably the route of infection in these patients is a shared venous plexus between the pelvis and spine. Injection drug use-related infections typically occur in younger patients and may affect the cervical or lumbosacral spine. *P. aeruginosa* vertebral osteomyelitis is usually an indolent disease. Accordingly, symptoms may develop weeks or even months before diagnosis. Back or neck pain is generally reported, while fever and systemic symptoms are relatively uncommon. Local tenderness and decreased range of motion of the affected spine are typical. Leukocytosis may be noted, the erythrocyte sedimentation rate is almost always markedly elevated, and blood cultures are sometimes positive. Roentgenograms reveal loss of bone density, narrowed intervertebral space, destruction of vertebral end plates, lytic lesions of vertebral bodies, sclerosis, and occasionally osteophyte formation.CT andMRI are the most sensitive and specific means of defining lesions. Technetium bone scans and gallium scans usually yield positive results. An etiologic diagnosis requires the culture of material obtained by needle aspiration or biopsy of the affected spine under fluoroscopic guidance; open biopsy is sometimes needed.

Sternoclavicular pyarthrosis caused by *P. aeruginosa* is another complication of injection drug use; in some cases it is associated with *P. aeruginosa* endocarditis, but more often it is not. Joint involvement is usually monoarticular, with the sternoclavicular joint more often affected than sternochondral joints. Patients present with acute or chronic pain in the anterior chest wall, often associated with fever and restricted movement of the homolateral shoulder. Physical examination reveals tenderness, erythema, and swelling over the affected joint. Leukocytosis is common, and the erythrocyte sedimentation rate is almost invariably elevated. Roentgenograms show soft tissue edema; bone demineralization; lytic lesions; and periosteal elevation of the clavicular head, rib, or sternum. Material obtained by arthrocentesis or synovial biopsy yields *P. aeruginosa* in culture.

*P. aeruginosa* infections of the symphysis pubis are associated with pelvic surgery and injection drug use. The symphysis pubis, like other fibrocartilaginous joints, exhibits a peculiar susceptibility to bloodborne infection with *P. aeruginosa*. Affected patients report pain in the groin, hip, thigh, and/or lower abdomen that is made worse by walking. Fever is variable, and the duration of symptoms before diagnosis ranges from days to

months. The erythrocyte sedimentation rate is markedly elevated. Roentgenography orCT shows irregularities of the pubic margins, separation of the symphysis pubis, and osteomyelitic abnormalities of the pubic rami that may be extensive. Bone scans are usually positive. Needle aspiration or biopsy is necessary to obtain material for culture. A positive culture is particularly important for the discrimination of *P. aeruginosa* infections and other pyogenic infections from osteitis pubis, which is thought to be a noninfectious condition complicating pelvic surgery, childbirth, or trauma.

*P. aeruginosa* osteochondritis of the foot follows puncture wounds of the foot, primarily in children. The organism infects the small joints and bones, including the proximal phalanges, metatarsals, metatarsophalangeal joints, tarsal bones, and calcaneus. On average, local pain and swelling last for several weeks, and systemic symptoms are usually lacking. There may be plantar cellulitis over the involved area or tenderness upon deep palpation. Results of roentgenograms and bone scans are generally positive. Aspiration of the affected joint frequently yields purulent material in which *P. aeruginosa* can be demonstrated by Gram's staining and by culture.

*P. aeruginosa* is one of the most common causative agents in a variety of other, less specific syndromes involving nonhematogenous infections of bones and joints and collectively referred to as *chronic contiguous osteomyelitis*. These infections may result, for example, from compound fractures, contamination associated with open reduction and fixation of closed fractures, sternotomy performed in conjunction with cardiac surgery, contiguous spread from infected ischemic ulcers related to peripheral vascular disease or diabetes mellitus, and cellulitis in general. The chronicity, indolence, and heterogeneity of these infections explain their varied clinical manifestations and the frequent need for complicated long-term management.

**Urinary Tract Infections** *P. aeruginosa* is one of the most common causes of complicated and nosocomial infections of the urinary tract. These infections may result from urinary tract catheterization, instrumentation, surgery, or obstruction; they may arise from persistent foci (e.g., the prostate or stones) and may be chronic or recurrent. The urinary tract may be a target for bloodborne infection in patients with *P. aeruginosa* bacteremia but more often is the source of bacteremia. Chronic *P. aeruginosa* infections of the urinary tract are relatively common among patients with indwelling urinary catheters, altered urinary tract anatomy secondary to diversionary procedures, and paraplegia.

The clinical features of urinary tract infections due to *P. aeruginosa* are usually indistinguishable from those of other bacterial infections. However, *P. aeruginosa* infections exhibit a propensity for persistence, chronicity, resistance to antibiotic therapy, and recurrence. More unusual forms of urinary tract involvement peculiar to *P. aeruginosa* include (1) ulcerative lesions of the renal pelvis, ureters, and bladder that cause sloughing of vesical membranes in the urine; and (2) ecthyma-like lesions of the renal cortex that are seen in association with *Pseudomonas* sepsis.

**Skin and Soft Tissue Infections** As indicated above, *P. aeruginosa* bacteremia may be associated with the disseminated skin lesions of ecthyma gangrenosum (seePlate IID-57C). Less common skin manifestations of *P. aeruginosa* sepsis include vesicular or pustular lesions, bullae, subcutaneous nodules, deep abscesses, and cellulitis.

Metastatic lesions of the skin or mucous membranes complicate *Pseudomonas* sepsis and occasionally produce massive necrosis or gangrene of the extremities, perineum, face, or oropharynx.

Primary *P. aeruginosa* pyoderma occurs when the skin breaks down secondary to trauma, burn injury, dermatitis, or ulcers related to peripheral vascular disease or pressure sores. Moist conditions and neutropenia may predispose to this condition. The clinical appearance of primary *P. aeruginosa* pyoderma, which frequently includes hemorrhage and necrosis, resembles that of metastatic *P. aeruginosa* skin lesions. Histologic studies document vascular invasion by bacteria in both diseases. A rare distinguishing feature of *P. aeruginosa* pyoderma is its association with a blue-green exudate and a characteristic fruity odor.

*P. aeruginosa* wound sepsis complicating extensive third-degree burn injuries is associated with an extremely high mortality rate. This infection results from colonization of the burn site or burn eschar, invasion of the subeschar space and underlying dermis, vascular invasion, and systemic spread. The development and progression of *P. aeruginosa* burn wound sepsis are facilitated by the injury-associated breakdown of normal skin, selection of empirical antibiotics with inadequate coverage for this pathogen, and burn-related immune defects. Local manifestations include black, dark brown, or violaceous discoloration of the burn eschar; degeneration of underlying granulation tissue, hemorrhage, and premature eschar separation; edema, hemorrhage, and necrosis of skin adjacent to the burn site; and erythematous nodular lesions in unburned skin. Systemic manifestations include fever or hypothermia and other signs of sepsis,SIRS, or multiple-organ system failure. The diagnosis of *P. aeruginosa* burn sepsis is based on these local and systemic clinical manifestations and on a burn wound biopsy that reveals both>$10^5$colony-forming units of *P. aeruginosa* per gram of tissue and histologic evidence of bacterial invasion of unburned tissue, vasculitis, or intense inflammation at the burn margin.

*P. aeruginosa* causes diffuse pruritic maculopapular and vesiculopustular rashes associated with exposure to contaminated hot tubs (Fig. 128-CD4), spas, whirlpools, and swimming pools. Many cases of *P. aeruginosa* dermatitis have occurred in conjunction with a common-source outbreak. At least two nosocomial common-source outbreaks -- one related to a physiotherapy pool -- have been reported. Skin rashes may be limited to areas covered by swimsuits or may be more diffuse, sparing only the head and neck. Low-grade fever or other associated symptoms are uncommon. The illness is usually self-limited, and the rash resolves without specific therapy after cessation of exposure.

***P. aeruginosa* Infections in Patients with AIDS** During the 1980s and 1990s, *P. aeruginosa* infections were increasingly associated with AIDS. The vast majority of these infections are currently seen in patients with advanced AIDS, previous opportunistic infections, and CD4+ lymphocyte counts<100/uL (often<50/uL). The specific immunologic factors that lead to *P. aeruginosa* infections in patients with AIDS are not well understood but are speculated to be a loss of mucosal integrity, defects in cellular and humoral immunity, and qualitative leukocyte abnormalities. Of note is that the majority of *P. aeruginosa* infections in this population are community-acquired, in contrast to the nosocomial transmission documented for most *P. aeruginosa* infections

in non-AIDS patients.

Pneumonia accounts for a substantial proportion of the *P. aeruginosa* infections in patients with AIDS. In most instances, pneumonia presents as a necrotizing infection of the pulmonary parenchyma, frequently with cavitary lesions, or as a chronic relapsing bronchopulmonary infection reminiscent of the bronchopulmonary disease seen in patients with cystic fibrosis. Also frequent are bloodstream infections, including those associated with indwelling central venous catheters, and infections of the paranasal sinuses, skin and soft tissue, and urinary tract. Bacteremia, either primary or secondary to infection at a remote site, is often recurrent, associated with high mortality, and occasionally accompanied by skin manifestations similar to those seen in non-AIDS patients.

Because *P. aeruginosa* infections occur in patients with advanced AIDS, survival after recovery from the initial infection may be limited to a few months. However, with the widespread use of highly active antiretroviral therapy and the consequent increase in CD4+ cell counts, the incidence of *P. aeruginosa* infection in patients with AIDS is likely to decline and the natural history of infection to change. For example, a few patients with recalcitrant, relapsing *P. aeruginosa* bronchopulmonary infections have reportedly experienced the resolution of infection soon after initiation of intensive antiretroviral therapy.

**TREATMENT**

Table 155-2 lists antimicrobial agents available in the United States that are generally active against *P. aeruginosa*.Table 155-3 outlines suggested antibiotic choices and an approach to therapy for selected sites of infection. The initial antibiotic selection should take into account the local patterns of antimicrobial susceptibility, while the susceptibilities of the isolate from a particular case should guide definitive antibiotic therapy.

In most severe or life-threatening infections due to *P. aeruginosa*, two antipseudomonal antibiotics to which the infecting strain is (or is likely to be) sensitive should be administered together. The benefits of this combined therapy, as determined by in vitro studies, are to increase efficacy, to achieve additive or synergistic killing, and to prevent the emergence of antibiotic resistance. Despite widespread acceptance of combination therapy for *P. aeruginosa* infections, there are few clinical data since the advent of newerb-lactam antibiotics documenting that combination therapy is more efficacious than monotherapy or that it actually forestalls the acquisition of antimicrobial resistance. Nevertheless, combination therapy continues to be recommended for most acute or fulminant infections, as outlined in Table 155-3.

The appropriate duration of antibiotic therapy for disease caused by *P. aeruginosa* depends on the type, location, and severity of infection. In general, chronic infections associated with extensive tissue injury, disruption of normal anatomy, foreign or prosthetic material, or suboptimal antibiotic accessibility require therapy for weeks or even months rather than days. More acute infections may be treated aggressively but for shorter periods.

*P. aeruginosa* infections of the lower respiratory tract in cystic fibrosis pose a special challenge because of their long-standing nature. In general, antibiotic therapy for acute exacerbations results in short-term clinical improvement, while periodic expectant courses of antimicrobial therapy may limit disease progression. A more novel approach utilizing intermittent, cyclical administration of inhaled tobramycin has been shown to improve pulmonary function, decrease the risk of hospitalization, and reduce the density of *P. aeruginosa* in sputum of older patients with cystic fibrosis. Lung transplantation has also been employed with good results in selected cystic fibrosis patients with severe, progressive lower respiratory tract infections due to *P. aeruginosa*.

## ANTIMICROBIAL RESISTANCE

Antibiotic resistance in *P. aeruginosa* is both intrinsic, as reflected by the relative paucity of antibiotics with inherent antimicrobial activity against wild-type strains, and acquired, as defined by high-level resistance to agents that would be expected to exhibit antimicrobial activity. Acquired resistance is rapidly increasing among *P. aeruginosa* isolates, particularly those associated with cystic fibrosis and with intensive care units. Escalating resistance among intensive care unit isolates is especially alarming. Data from theNNISsystem show an increase in rates of resistance to imipenem and fluoroquinolones from 12% during previous years to 18.5% and 23.0%, respectively, during 1999. Factors responsible for this increase may include expanding use of immunosuppressive therapies, increased severity of illness in hospitalized patients, inadequate infection control procedures, and growing antibiotic use. Resistant organisms can be transmitted directly to patients from the hospital staff, other patients, or the environment, or they may arise de novo during therapy with any given agent. Emergence of multi-drug-resistant strains has been associated with increases in secondary bacteremia and mortality and has led in some cases to longer hospital stays and increased hospitalization costs. Therapy for patients with resistant *P. aeruginosa* infections should consist of antimicrobial agents selected on the basis of extended susceptibility testing. Increased treatment duration and surgical drainage or removal of infected tissues may be necessary.

## INFECTIONS CAUSED BY OTHER *PSEUDOMONAS* SPECIES OR RELATED BACTERIA

***Burkholderia cepacia*** *B. cepacia*, like *P. aeruginosa*, is primarily an opportunistic pathogen that is implicated in both sporadic endemic infections and occasional nosocomial outbreaks. Hospital epidemics are most frequently associated with a liquid reservoir or a moist environmental surface. Colonization by *B. cepacia* precedes infection, and distinction between the two is often difficult. *B. cepacia* has been reported to cause pneumonia, urinary tract infections, meningitis, peritonitis, surgical and burn wound infections, bacteremia, and endocarditis related to injection drug use. In addition, *B. cepacia* has been implicated as a cause of chronic lower respiratory tract infections in patients with chronic granulomatous disease, in patients with sickle cell hemoglobinopathies, and -- together with *P. aeruginosa* -- in patients with cystic fibrosis. In some patients with cystic fibrosis, the appearance of *B. cepacia* has been associated with fulminant necrotizing pneumonia, bacteremia, and a rapid downhill course.

## TREATMENT

The treatment of *B. cepacia* infections is complicated by intrinsic resistance of the organism to aminoglycosides and many b-lactam agents. Although trimethoprim-sulfamethoxazole and chloramphenicol have been used successfully in the treatment of *B. cepacia* infections, resistance to these two antimicrobial agents has been reported. Carbapenems, third-generation cephalosporins, and fluoroquinolones may offer activity against sensitive strains, but relevant clinical experience is limited. Some but not all cystic fibrosis centers segregate patients infected with *B. cepacia* in an attempt to reduce horizontal transmission to uninfected patients. In addition, many centers consider lung transplantation contraindicated in these patients because of an unacceptably high mortality rate after surgery.

***Stenotrophomonas maltophilia*** *S. maltophilia* is a ubiquitous, free-living opportunistic bacterium that has emerged as an important pathogen in hospitalized patients, particularly in cancer centers and intensive care units. Factors that lead to colonization and infection include prolonged hospitalization, malignancy, instrumentation (including urinary, peritoneal, and central venous catheterization), and prior administration of broad-spectrum antibiotics. This organism has most commonly been associated with pneumonia but also causes bacteremia, urinary tract infection, wound infection, peritonitis, cholangitis, meningitis, and (rarely) endocarditis. Acute *S. maltophilia* pneumonia -- an often devastating disease associated with bacteremia -- is being seen with increasing frequency in debilitated patients on intensive care units. Antibiotic resistance in *S. maltophilia*, based on both low outer-membrane permeability and inducible b-lactamases, is at least partly responsible for the emergence of this organism as a nosocomial pathogen under the selective pressure of antibiotic treatment.

## TREATMENT

Trimethoprim-sulfamethoxazole (at a trimethoprim dose of 15 to 20 mg/kg per day for patients with normal renal function) is the drug of choice for treatment of most *S. maltophilia* infections. Alternative agents include ticarcillin/clavulanate, minocycline, and doxycycline. The third-generation cephalosporins cefoperazone and ceftazidime are occasionally active against *S. maltophilia*, but in vitro susceptibilities may not reflect clinical efficacy. The aminoglycosides and imipenem are almost always inactive. Indwelling catheters or appliances that are associated with infection should be removed.

**Melioidosis** Infections caused by *B. pseudomallei* constitute a broad spectrum of acute and chronic, local and systemic, clinical and subclinical disease processes collectively called *melioidosis*. *B. pseudomallei* and the infections it causes are found mainly in the tropics and are endemic in Southeast Asia and surrounding areas. *B. pseudomallei* is a free-living, small, motile, aerobic, gram-negative bacillary saprophyte normally found in soil, ponds, and rice paddies and on produce from endemic areas. It is occasionally a pathogen for animals. Humans contract the disease through soil contamination of abrasions, ingestion, or inhalation. In contrast to *B. cepacia*, *B. pseudomallei* does not establish colonization without causing infection and is rarely transmitted from person to person.

Melioidosis presents in different forms. High rates of seropositivity in endemic areas such as Vietnam, Thailand, and Malaysia suggest that many infections are clinically

inapparent. The occasional diagnosis based solely on abnormal routine chest roentgenograms represents asymptomatic pneumonitis. Acute pulmonary infections may originate in the respiratory tract or result from hematogenous spread, their severity varying from mild bronchitis to extensive necrotizing pneumonia. Onset may be sudden or gradual. Fever, productive cough, and marked tachypnea are frequent. Chest roentgenograms typically reveal upper-lobe infiltrates or thin-walled cavities that may mimic tuberculosis. Acute, localized, suppurative skin infections associated with nodular lymphangitis and regional lymphadenitis result from direct inoculation at sites of minor skin trauma. Recrudescent disease arising from inactive sites of infection and perhaps triggered by intercurrent illness or other events may present in an acute or chronic form.

Either acute suppurative infections or pulmonary disease may give rise to hematogenous dissemination and the acute septicemic form of melioidosis. This progression is more likely in chronically debilitated patients, such as those with diabetes mellitus or alcoholism. Septicemic patients may present with severe tachypnea, confusion, headache, pharyngitis, diarrhea, and pustular lesions of the head, trunk, and extremities. The skin may be flushed or cyanotic, signs of meningitis or arthritis may be apparent, the liver and spleen may be enlarged, and muscle tenderness may be striking. Chest roentgenograms show diffuse nodular densities that may expand, coalesce, and finally cavitate. The acute septicemic form of melioidosis usually follows a rapid downhill course, ending in early death. Mortality remains high despite optimal therapy.

The diagnosis of melioidosis should be entertained when a febrile patient who has been in an endemic area presents with an acute lower respiratory tract illness associated with tachypnea, exhibits unusual skin or subcutaneous lesions, or has a chest roentgenogram suggesting tuberculosis in the absence of sputum-associated tubercle bacilli. An etiologic diagnosis may be made by microscopic demonstration of small, irregularly staining, gram-negative rods in exudate material; by characteristic bipolar ("safety-pin") staining of organisms with methylene blue; and by a culture positive for *B. pseudomallei* and/or a fourfold or greater rise in the titer of serum antibody to the organism.

**TREATMENT**

The mainstay of treatment for melioidosis is antibiotic administration combined with appropriate surgical drainage of abscesses and aggressive support for patients with septicemic forms of the disease. The guidelines for antibiotic therapy are somewhat imprecise. Subclinical infection or mere seropositivity does not usually require specific therapy. Ceftazidime or imipenem appears to be the agent of choice for clinical disease, including severe infections, while trimethoprim-sulfamethoxazole, cefotaxime, and amoxicillin/clavulanate are possible alternatives. Combination therapy with ceftazidime or imipenem plus trimethoprim-sulfamethoxazole may be indicated in severe forms of melioidosis, including septicemia. Unfortunately, increasing resistance of many strains of *B. pseudomallei* to trimethoprim-sulfamethoxazole, particularly in Southeast Asia, is of concern. Patients with acute pulmonary infections who are treated with either ceftazidime or imipenem should receive antibiotics until they show definite evidence of clinical improvement (often after 10 to 30 days), at which time therapy can be switched to an oral maintenance regimen -- a combination of chloramphenicol,

trimethoprim-sulfamethoxazole, and doxycycline or the single agent amoxicillin/clavulanate -- and continued for 12 to 20 weeks. Chronic disease associated with persistently positive sputum cultures and extrapulmonary suppurative disease may require treatment for up to 1 year.

**Other Species** *Pseudomonas fluorescens* occasionally causes human disease; it is implicated particularly often in infections related to the administration of contaminated (stored) blood products and in pseudoinfections. Additional species that are associated only rarely with human infections include *P. putida*, *P. stutzeri*, *P. pseudoalcaligenes*, and (all formerly *Pseudomonas* species) *Burkholderia gladioli*, *B. pickettii*, *Comamonas acidovorans*, *C. testosteroni*, *Brevundimonas diminuta*, and *B. vesicularis*.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 156. SALMONELLOSIS - *Cammie F. Lesser*, *Samuel I. Miller*

The salmonellae constitute a genus of over 2300 serotypes that are highly adapted for growth in both human and animal hosts and cause a wide spectrum of disease. A subset of *Salmonella* serotypes that includes *S. typhi* and *S. paratyphi* causes enteric (typhoid) fever and is restricted to growth in human hosts. The remainder of *Salmonella* serotypes, referred to as nontyphoidal *Salmonella*, are prevalent in the gastrointestinal tracts of a broad range of animals, including mammals, reptiles, birds, and insects. Over 200 of these serotypes are pathogenic to humans; these pathogenic serotypes cause gastroenteritis and can be associated with localized infections and/or bacteremia.

### ETIOLOGY

*Salmonella* is a large genus of gram-negative bacilli within the family Enterobacteriaceae. The nomenclature and classification of these bacteria have undergone numerous revisions, most recently in 1983 when -- on the basis of a high degree of DNA similarity between the bacterial genomes -- over 2000 bacterial strains were grouped into one species, *S. choleraesuis*. This species was further divided into seven subgroups based on host range specificity and additional DNA similarity. Almost all the strains pathogenic for humans are in subgroup 1 (*enterica* or *choleraesuis*) except for those causing rare infections (subgroups 3a and 3b). The nomenclature of this large species is quite complex. For example, the correct taxonomic name for the organism that causes enteric fever is *Salmonella choleraesuis* ssp. *choleraesuis* (or subgroup 1), serovar *typhi*. Given the cumbersome nature of this nomenclature system, a simplified system is in widespread use, in which the common species name that existed before the reclassification of the species is accepted. For example, *S. choleraesuis* ssp. *choleraesuis*, serovar *typhi*, is referred to by its common name, *S. typhi*.

The initial identification of this genus in the clinical laboratory relies on growth characteristics. Like other Enterobacteriaceae, salmonellae produce acid on glucose fermentation, reduce nitrates, and do not produce cytochrome oxidase. They are non-spore-forming and facultatively anaerobic. With few exceptions, salmonellae are motile by means of peritrichous flagella (exception: *S. gallinarum-pullorum*) and produce gas ($H_2S$) on sugar fermentation (exception: *S. typhi*). Since 99% of clinical isolates are lactose nonfermenters, rare clinical isolates may not be detected if a high level of suspicion is not maintained.

*Salmonella* can be further divided into serovars based on the detection of three major antigenic determinants: the somatic O antigen [lipopolysaccharide (LPS) cell-wall components], the surface Vi antigen (restricted to *S. typhi* and *S. paratyphi* C), and the flagellar H antigen. In general, clinical laboratories initially divide *Salmonella* into serogroups (A, B, $C_1$, $C_2$, D, and E) based on reactivity to somatic O-antigen antisera. These initial groupings provide only limited clinical information, given their high degree of cross-reactivity. Thus, additional biochemical and serologic tests are needed to determine serotype. For the epidemiologic evaluation of *Salmonella* outbreaks, specific *Salmonella* strains within serovars can be distinguished by bacteriophage typing, plasmid profile determination, and restriction length polymorphism analysis.

## PATHOGENESIS

Salmonellae are transmitted to humans orally by contaminated food or water. The bacteria traverse the gastrointestinal tract, including the acidic environment of the stomach, to colonize the small intestines. In the case of enteric fever (a systemic illness), salmonellae cross the intestinal barrier, where phagocytosis by macrophages results in their dissemination throughout the reticuloendothelial system. In nontyphoidal salmonellosis, the bacteria generally cause a localized infection resulting in an influx of neutrophils to the intestines and self-limited gastroenteritis.

Numerous attempts have been made to determine the infectious dose ($ID_{50}$) of *Salmonella*, both in the laboratory and in the field. Controlled experiments, in which healthy volunteers were exposed to laboratory-grown strains of *S. typhi*, concluded that the $ID_{50}$ was $10_6$colony-forming units (CFU); increases in the $ID_{50}$corresponded to decreases in incubation time. However, analyses of salmonellosis outbreaks with a known source indicate that the $ID_{50}$ can be as low as $10_3$ CFU. Host defenses, the most important of which appears to be the acidity of the stomach, most likely account for variations in the $ID_{50}$. Conditions that decrease stomach acidity (an age of<1 year, antacid ingestion, or achlorhydric disease) increase susceptibility to *Salmonella* infection, as do conditions that decrease intestinal integrity (inflammatory bowel disease, history of gastrointestinal surgery, or alteration of the intestinal flora by antibiotic administration).

Once salmonellae reach the small intestine, the bacteria resist a variety of innate immune factors (including bile salts, lysozyme, complement, and cationic antimicrobial peptides) before penetrating the mucus layer. The organisms enter the intestines through phagocytic microfold or M cells overlying the Peyer's patches. Salmonellae also enter normally nonphagocytic epithelial cells by a process known as *bacteria-mediated endocytosis*, whose mechanism is not entirely clear but depends on the direct translocation of *Salmonella* proteins into the host cell cytoplasm by a specialized secretion apparatus (type III secretion).

In enteric (typhoid) fever, salmonellae (*S. typhi* or *S. paratyphi*) undergo phagocytosis by macrophages after crossing the epithelial layer of the small intestine. Once phagocytosed, the bacteria are protected from polymorphonuclear leukocytes (PMNs), the complement system, and the acquired immune response (antibodies). Salmonellae have evolved mechanisms to avoid or delay killing by macrophages. Upon phagocytosis, the bacteria form a "spacious phagosome" and alter the regulation of ~200 bacterial proteins. The best-characterized regulatory system is PhoP/PhoQ, a two-component regulon that senses changes in bacterial location and alters bacterial protein expression. The alterations mediated by PhoP/PhoQ include modifications inLPS and in the synthesis of outer-membrane proteins; these changes presumably remodel the bacteria's outer surface such that the organisms can resist microbicidal activities and possibly alter host cell signaling. PhoP/PhoQ also mediates the synthesis of divalent cationic transporters that scavenge magnesium. By a second type III secretion mechanism, salmonellae can directly translocate bacterial proteins into the macrophage, a phenomenon that is believed to promote survival within phagocytes.

After phagocytosis, salmonellae disseminate throughout the body in macrophages via

the lymphatics and colonize reticuloendothelial tissues (liver, spleen, lymph nodes, and bone marrow). During this initial incubation stage, patients are relatively asymptomatic. Signs and symptoms, including fever and abdominal pain, probably result from secretion of cytokines by macrophages when a critical number of organisms have replicated. For example, the observed hepatosplenomegaly is likely to be related to the recruitment of mononuclear cells and the development of a cell-mediated immune response to *S. typhi* colonization. The recruitment of additional mononuclear cells and lymphocytes to Peyer's patches during the several weeks after initial colonization/infection can result in marked enlargement and necrosis of the Peyer's patches, with right-lower-quadrant abdominal pain.

It is not known why *S. typhi* and *S. paratyphi* cause systemic disease while the vast majority of pathogenic *Salmonella* strains cause gastroenteritis. In contrast to enteric fever, which is characterized by an infiltration of mononuclear cells into the small-bowel mucosa, nontyphoidal *Salmonella* gastroenteritis is characterized by massivePMNinfiltration into both the large- and the small-bowel mucosa. This response appears to depend on the induction of interleukin (IL) 8, a strong neutrophil chemotactic factor, which is secreted by intestinal cells. The degranulation and release of toxic substances by neutrophils may result in damage to the intestinal mucosa, causing inflammatory diarrhea.

## ENTERIC (TYPHOID) FEVER

Typhoid fever is a systemic disease characterized by fever and abdominal pain caused by dissemination of *S. typhi* or *S. paratyphi*. The disease was initially called *typhoid fever* because of its clinical similarity to typhus. However, in the early 1800s, typhoid fever was clearly defined pathologically as a unique illness on the basis of its association with enlarged Peyer's patches and mesenteric lymph nodes. In 1869, given the anatomic site of infection, the term *enteric fever* was proposed as an alternative designation to distinguish typhoid fever from typhus. However, to this day, the two designations are used interchangeably.

### EPIDEMIOLOGY

In contrast to other *Salmonella* serotypes, the etiologic agents of enteric fever -- *S. typhi* and *S. paratyphi* -- have no known hosts other than humans. Thus, enteric fever is transmitted only through close contact with acutely infected individuals or chronic carriers. While direct person-to-person transmission through the fecal-oral route has been documented, it is quite rare. Rather, most cases of disease result from ingestion of contaminated food or water. Health care workers occasionally acquire enteric fever after exposure to infected patients, while laboratory workers can acquire the disease after laboratory accidents.

Over the past four decades, with the advent of improvements in food handling and water/sewage treatment, enteric fever has become a rare occurrence in developed nations. Over the past 10 years, ~400 cases of typhoid fever and even fewer cases of paratyphoid fever have been reported annually in the United States. In contrast, enteric fever continues to be a global health problem, with an estimated 13 to 17 million cases worldwide resulting in ~600,000 deaths per year. Children<1 year of age appear to be

most susceptible to initial infection and to the development of severe disease.

Enteric fever is endemic in most developing regions, especially the Indian subcontinent, South and Central America, and Asia, and is related to rapid population growth, increased urbanization, inadequate human waste treatment, limited water supply, and overburdened health care systems. These conditions most likely account for the recent epidemics of typhoid fever in eastern Europe. Antibiotic resistance among salmonellae is also a rising concern and has recently been linked to antibiotic use in livestock. Many *S. typhi* strains contain plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim -- the antibiotics that have long been used to treat enteric fever. In addition, resistance to ciprofloxacin, either chromosomally or plasmid encoded, has been observed in Asia. Morbidity and mortality are increased in outbreaks associated with antibiotic-resistant strains, presumably because of inadequate or delayed appropriate treatment.

The high worldwide prevalence of enteric fever serves as a reservoir for cases in the United States. Over 70% of U.S. cases are related to international travel within 30 days before onset. Only 3% of travelers diagnosed with enteric fever give a history of vaccination against *S. typhi* within the previous 2 years. Of U.S. cases of internationally acquired enteric fever, 80% can be linked to travel in six countries: Mexico (28%), India (25%), the Philippines (10%), Pakistan (8%), El Salvador (5%), and Haiti (4%). While the percentage of cases associated with travel to Mexico is declining, travel to the Indian subcontinent is becoming much riskier, with an incidence 18 times higher than for any other area. The recent trend toward an increased incidence of multidrug-resistant (MDR) *Salmonella* (see "Treatment," below) in developing countries is reflected by the increase in the proportion of U.S. cases caused by MDR strains from 0.6% in 1985-1989 to 12% in 1990-1994.

Almost 30% of the reported cases of enteric fever in the United States are domestically acquired. Although the majority of these cases (80%) are sporadic, large outbreaks do occur. In the most notable outbreak in the past 15 years, 47 culture-proven and 24 potential cases were linked to contaminated orange juice at a resort in New York. Evaluation of this outbreak led to the identification of a previously unknown chronic carrier. Similarly, evaluation of 25% of the 571 cases of domestically acquired enteric fever reported between 1985 and 1994 led to the identification of previously unknown chronic carriers.

## CLINICAL COURSE

Enteric fever is a misnomer, in that the hallmark features of this disease -- fever and abdominal pain -- are variable. While fever is documented at presentation in >75% of cases, abdominal pain is reported in only 20 to 40%. Thus, a high index of suspicion for this potentially lethal systemic illness is necessary when a person presents with fever and a history of recent travel to a developing country.

The incubation period for *S. typhi* ranges from 3 to 21 days. This variability is most likely related to the size of the initial inoculum and the health and immune status of the host. The most prominent symptom of this systemic infection is prolonged fever (38.8° to 40.5°C, or 101.8° to 104.9°F). A prodrome of nonspecific symptoms often precedes

fever and includes chills, headache, anorexia, cough, weakness, sore throat, dizziness, and muscle pains. Gastrointestinal symptoms are quite variable. Patients can present with either diarrhea or constipation; diarrhea is more common among patients with AIDS and among children<1 year of age. As stated above, only 20 to 40% of patients present with abdominal pain, although the majority have abdominal tenderness over the course of the disease. In general, the symptoms associated with *S. typhi* are more severe than those associated with *S. paratyphi*.

Early physical findings of enteric fever include rash ("rose spots"), hepatosplenomegaly, epistaxis, and relative bradycardia. Rose spots make up a faint, salmon-colored, blanching, maculopapular rash located primarily on the trunk and chest. The rash is evident in ~30% of patients at the end of the first week and resolves after 2 to 5 days without leaving a trace. Patients can have two or three crops of lesions, and *Salmonella* can be cultured from punch biopsies of these lesions. The faintness of the rash makes it difficult to detect in dark-skinned patients. On occasion, patients who remain toxic manifest neuropsychiatric symptoms described as a "muttering delirium" or "coma vigil," with picking at bedclothes or imaginary objects.

Late complications, occurring in the third and fourth weeks of infection, are most common in untreated adults and include intestinal perforation and/or gastrointestinal hemorrhage. These complications can develop despite clinical improvement and presumably result from necrosis at the initial site of *Salmonella* infiltration in the Peyer's patches of the small intestine. Both complications are life-threatening and require immediate medical and surgical interventions, with broadened antibiotic coverage for polymicrobial peritonitis (Chap. 130) and treatment of gastrointestinal hemorrhages, including bowel resection.

Rare complications whose incidences are reduced by prompt antibiotic treatment include pancreatitis, hepatic and splenic abscesses, endocarditis, pericarditis, orchitis, hepatitis, meningitis, nephritis, myocarditis, pneumonia, arthritis, osteomyelitis, and parotitis. Despite prompt antibiotic treatment, relapse rates remain at ~10% in immunocompetent hosts.

Approximately 1 to 5% of patients with enteric fever become long-term, asymptomatic, chronic carriers who shed *S. typhi* in either urine or stool for >1 year. The incidence of chronic carriage is higher among women and among persons with biliary abnormalities (e.g., gallstones, carcinoma of the gallbladder) and gastrointestinal malignancies. The anatomic abnormalities associated with these conditions presumably allow prolonged colonization.

## DIAGNOSIS

Other than a positive culture, no specific laboratory test is diagnostic for enteric fever. In 15 to 25% of cases, leukopenia and neutropenia are detectable. In the majority of cases, the white blood cell count is normal despite high fever. However, leukocytosis can develop in typhoid fever (especially in children) during the first 10 days of the illness, or later if the disease course is complicated by intestinal perforation or secondary infection. Other nonspecific laboratory results include moderately elevated values in liver function tests (aminotransferases, alkaline phosphatase, and lactate

dehydrogenase). In addition, nonspecific ST and T wave abnormalities can be seen on electrocardiograms.

The diagnostic "gold standard" is a culture positive for *S. typhi* or *S. paratyphi*. The yield of blood cultures is quite variable: it can be as high as 90% during the first week of infection and decrease to 50% by the third week. A low yield is related to low numbers of *Salmonella* (<15 organisms per milliliter) in infected patients and/or to recent antibiotic treatment. Centrifugation to isolate and culture the buffy coat, which contains abundant blood mononuclear cells associated with the bacteria, decreases time to isolation but does not affect culture sensitivity.

A diagnosis can also be based on positive cultures of stool, urine, rose spots, bone marrow, and gastric or intestinal secretions. Unlike blood cultures, bone marrow cultures remain highly (90%) sensitive despite £5 days of antibiotic therapy. Culture of intestinal secretions (best obtained by a noninvasive duodenal string test) can be positive despite a negative bone marrow culture. If blood, bone marrow, and intestinal secretions are all cultured, the yield of a positive culture is >90%. Stool cultures, while negative in 60 to 70% of cases during the first week, can become positive during the third week of infection in untreated patients. Although the majority of patients (90%) clear bacteria from the stool by the eighth week, a small percentage become chronic carriers and continue to have positive stool cultures for at least 1 year.

Several serologic tests, including the classic Widal test for "febrile agglutinins," are available; however, given high rates of false-positivity and false-negativity, these tests are not clinically useful. Polymerase chain reaction and DNA probe assays are being developed.

**TREATMENT**

In the preantibiotic era, the mortality rate from typhoid fever was as high as 15%. The introduction of treatment with chloramphenicol in 1948 greatly altered the disease course, decreasing mortality to <1% and the duration of fever from 14-28 days to 3-5 days. Chloramphenicol remained the standard treatment for enteric fever until the emergence of plasmid-mediated resistance to this drug in the 1970s. Given the increased mortality associated with resistance to chloramphenicol and the rare chloramphenicol-induced bone marrow toxicity, ampicillin (1 g orally every 6 h) and trimethoprim-sulfamethoxazole (TMP-SMZ; one double-strength tablet twice daily) became the mainstays of treatment.

In 1989,MDR*S. typhi* emerged. These bacteria are resistant to chloramphenicol, ampicillin, trimethoprim, streptomycin, sulfonamides, and tetracycline. Like chloramphenicol resistance, resistance to ampicillin and trimethoprim is plasmid-encoded. In 1994, 12% of *S. typhi* isolates in the United States were MDR. Thus either quinolones or third-generation cephalosporins are currently recommended for empirical antibiotic treatment. Despite efficient in vitro killing of *Salmonella*, first- and second-generation cephalosporins as well as aminoglycosides are ineffective in treating clinical infections.

Ceftriaxone (1 to 2 g intravenously or intramuscularly) for 10 to 14 days is equivalent to

oral or intravenous chloramphenicol in the treatment of susceptible strains. Preliminary studies indicate that a 5- to 7-day course of ceftriaxone is likely to be sufficient for treatment of uncomplicated cases. However, one recent report describes a ceftriaxone-resistant *Salmonella* strain isolated from a child with diarrhea and apparently acquired from antibiotic-treated cattle.

Quinolones are the only available oral antibiotics for the treatment ofMDR*S. typhi* infections. The greatest experience has been gained for ciprofloxacin (500 mg orally twice a day for 10 days). Shorter courses of ofloxacin (10 to 15 mg/kg in divided doses twice daily for 2 to 3 days) have also been successful. However, quinolone resistance is emerging. In 1993, an outbreak of nalidixic acid-resistant *S. typhi* (NARST) infections in Vietnam was linked to chromosomal mutations in the gene encoding DNA gyrase (the target of the quinolones). NARST strains have also been isolated in India. Thus, all strains of *S. typhi* must be screened for resistance to nalidixic acid and tested for sensitivity to a clinically appropriate quinolone. Patients infected with NARST strains need to be treated with higher doses of ciprofloxacin (10 mg/kg twice a day for 10 days) or longer courses of ofloxacin (10 to 15 mg/kg in divided doses twice daily for 7 to 10 days) or with other antibiotics to which the strains are sensitive.

In cases of severe typhoid fever (fever; an abnormal state of consciousness -- i.e., delirium, obtundation, stupor, or coma -- or septic shock; and a positive culture for *S. typhi* or *S. paratyphi* A), dexamethasone treatment should be considered. In a single trial in Jakarta in the early 1980s in chloramphenicol-treated patients, treatment with dexamethasone (a single dose of 3 mg/kg followed by eight doses of 1 mg/kg, given every 6 h) decreased mortality from 56% to 10%.

The 1 to 4% of patients who develop chronic carriage of *Salmonella* can be treated for 6 weeks with an appropriate antibiotic. Treatment with oral amoxicillin,TMP-SMZ, ciprofloxacin, or norfloxacin has been shown to be ~80% effective in eradicating chronic carriage of susceptible organisms. However, in cases of anatomic abnormality (e.g., biliary or kidney stones), eradication of the infection often cannot be achieved by antibiotic therapy alone but also requires surgical correction of the abnormalities.

## PREVENTION AND CONTROL

Theoretically, it is possible to eliminate salmonellae that cause enteric fever since the bacteria survive only in human hosts and are spread by contaminated food and water. However, given the high prevalence of the disease in developing countries that lack good facilities for sewage disposal and water treatment, this goal is currently unrealistic. Thus, travelers to developing countries should be advised to monitor their food and water intake carefully and to consider vaccination.

Three vaccine alternatives are available: (1) a heat-killed, phenol-extracted, whole-cell vaccine (two parenteral doses); (2) Ty21a, an attenuated *S. typhi* vaccine (four oral doses); and (3) ViCPS, consisting of purified Vi polysaccharide from the bacterial capsule (one parenteral dose). In addition, an acetone-killed whole-cell vaccine is available only for use by the U.S. military. The minimal ages for vaccination with the whole-cell, Ty21a, and ViCPS vaccines are 6 years, 2 years, and 6 months, respectively. A large-scale meta-analysis of vaccine trials in populations of endemic

areas indicates that, while all three vaccines have similar efficacy for the first year, the 3-year cumulative efficacy of the whole-cell vaccine (73%) exceeds that of both Ty21a (51%) and purified Vi (55%). In addition, the heat-killed whole-cell vaccine maintains its efficacy for 5 years, while Ty21a and ViCPS most likely maintain their efficacy for 4 and 2 years, respectively. However, the whole-cell vaccine is associated with a much higher incidence of side effects than the other two vaccines: 16% of whole-cell vaccine recipients develop fever and 10% miss a day of work or school, while only 1 to 2% of persons receiving the alternative vaccines have any fever.

Although data on typhoid vaccines in travelers are limited, some evidence suggests that efficacy may be substantially lower than those for populations in endemic areas. The Centers for Disease Control and Prevention (CDC) currently recommends vaccination for persons traveling to developing countries who will have prolonged exposure to contaminated food and water or close contact with indigenous populations in rural areas. The only recommendations for domestic vaccination include people who have intimate or household contact with a chronic carrier or laboratory workers who frequently work with *S. typhi*. Given the decreased incidence of side effects and the similar short-term efficacy, the current bias is toward vaccination of travelers with either Ty21a or ViCPS.

Enteric fever is a reportable disease in the United States. This reporting system enables public health departments to track down potential source patients and thus to identify and treat chronic carriers in order to prevent further outbreaks. In addition, since 1 to 4% of patients with *S. typhi* infection become chronic carriers, it is important to monitor patients (especially those employed in child care or food handling) for chronic carriage and to treat this condition if indicated.

## NONTYPHOIDAL SALMONELLOSIS

### EPIDEMIOLOGY

The incidence of nontyphoidal salmonellosis has doubled in the United States over the past two decades. Currently, theCDCestimates that there are 2 million cases annually, with 500 to 2000 deaths. Although over 200 serovars of *Salmonella* are considered to be human pathogens, the majority of the reported cases in the United States is caused by *S. typhimurium* or *S. enteritidis*. The incidence of salmonellosis is highest during the rainy season in tropical climates and during the warmer months in temperate climates, coinciding with the peak in food-borne outbreaks. Morbidity and mortality associated with salmonellosis are highest among the elderly, infants, and immunocompromised individuals, including those with hemoglobinopathies and those infected with HIV or with pathogens that cause blockade of the reticuloendothelial system (e.g., patients with bartonellosis, malaria, schistosomiasis, or histoplasmosis).

Unlike *S. typhi* and *S. paratyphi*, whose only reservoir is humans, nontyphoidal salmonellosis is acquired from multiple animal reservoirs. The main mode of transmission is from food products contaminated with animal products or waste -- most commonly eggs and poultry but also undercooked meat, unpasteurized dairy products, seafood, and fresh produce.

*S. enteritidis* associated with chicken eggs is emerging as a major cause of food-borne disease. *S. enteritidis* causes infection of the ovaries and upper oviduct tissue of hens, resulting in contamination of the contents of eggs prior to shell deposition. Approximately 1 in 20,000 eggs is thought to be infected with *S. enteritidis*. Between 1974 and 1994, there was a fivefold increase (from 5% to 25%) in the isolation of *S. enteritidis* from eggs in the United States; in 1998, the U.S. Department of Agriculture estimated that 80% of all salmonellosis cases were caused by infected eggs. Eradication of *S. enteritidis* from hens has proven difficult, given that infection is spread to egg-laying hens both vertically from breeding flocks and horizontally through contact with rodents and manure. Transmission via contaminated eggs can be prevented by cooking of eggs such that the liquid yolk is solidified or through pasteurization of egg products.

Another factor in the increasing incidence of nontyphoidal salmonellosis in developed countries, including the United States, is related to the centralization of food processing and widespread distribution. For example, a 1994 outbreak of ~250,000 cases was linked to a pasteurized ice-cream premix most likely contaminated in tanker trucks that had previously carried unpasteurized eggs. Similar outbreaks have been traced to manufactured foods including pasteurized milk, infant formula, powdered-milk products, paprika-powdered potato chips, and a ready-to-eat savory snack. In addition, large outbreaks have been linked to fresh produce, including alfalfa sprouts, cantaloupe, fresh-squeezed orange juice, and sliced tomatoes, contaminated by manure or water at a single site and then broadly distributed.

A less common source of nontyphoidal *Salmonella* infections is exposure to exotic pets, especially reptiles. Fecal carriage rates in reptiles can be>90%. In the 1970s, 14% of cases of salmonellosis were attributed to small turtles; the distribution of these pets was subsequently prohibited by the U.S. Food and Drug Administration, with a resultant decline in rates of reptile-associated salmonellosis. However, since 1986, an increase in the popularity of nonbanned reptiles, including iguanas, has been followed by increases in rates of *Salmonella* infections. Other pets, including African hedgehogs, snakes, birds, rodents, baby chicks, ducklings, dogs, and cats, can also serve as potential vectors.

Antibiotic resistance is an increasing phenomenon among nontyphoidal *Salmonella* serovars. In particular, *S. typhimurium* of definitive phage type 104 (DT104) -- a serotype resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracyclines -- has become prominent in the United Kingdom. This serotype is associated with greater mortality and morbidity than other nontyphoidal *Salmonella* serotypes. Its acquisition is associated with exposure to ill farm animals and to a variety of meat products. The prevalence of *S. typhimurium* DT104 in the United States increased from 0.6% in 1979-1980 to 34% in 1996. Of concern is the isolation in the United Kingdom in 1996 of *S. typhimurium* DT104 strains resistant to ciprofloxacin (14%) or trimethoprim (24%).

## CLINICAL MANIFESTATIONS

**Gastroenteritis** Infection with nontyphoidal *Salmonella* most often results in gastroenteritis indistinguishable from that caused by other bacterial and viral pathogens.

Nausea, vomiting, and diarrhea occur 6 to 48 h after the ingestion of contaminated food or water. Patients often experience abdominal cramping and fever (38 to 39°C, or 100.5 to 102.2°F). The diarrhea is usually characterized as loose, nonbloody stools of moderate volume. However, large-volume watery stools, bloody stools, or symptoms of dysentery do not rule out the diagnosis. Rarely, *Salmonella* causes a syndrome of pseudoappendicitis or an illness that mimics inflammatory bowel disease.

Gastroenteritis caused by nontyphoidal *Salmonella* is usually self-limited. Diarrhea resolves within 3 to 7 days and fever within 72 h. Stool cultures remain positive for 4 to 5 weeks after infection and -- in rare cases of chronic carriage (<1%) -- remain positive for >1 year. Antibiotic treatment is usually not recommended and in some studies has prolonged carriage of *Salmonella*. Neonates, the elderly, and the immunosuppressed (e.g., HIV-infected patients) with nontyphoidal *Salmonella* gastroenteritis are especially susceptible to dehydration and dissemination and may require hospitalization and antibiotic therapy.

**Bacteremia and Endovascular Infections** Up to 5% of patients with nontyphoidal *Salmonella* gastroenteritis have positive blood cultures, and 5 to 10% of these bacteremic persons develop localized infections. Bacteremia is particularly common and persistent among infants, the elderly, and patients with severe underlying infection or immunosuppression (e.g., transplant recipients, HIV-infected patients). Salmonellae have a propensity for infection of vascular sites; if>50% of three or more blood cultures are positive, an endovascular infection should be suspected. Preexisting valvular heart disease is a strong risk factor for the development of endocarditis, while atherosclerotic plaque, prosthetic grafts, and aortic aneurysms are associated with arteritis. Arteritis should be suspected in elderly patients who have a history of prolonged fever with associated back, chest, or abdominal pain preceded by gastroenteritis. Endocarditis and arteritis are rare (<1% of cases) but are associated with potentially morbid complications. Endocarditis can be complicated by cardiac valve perforation or by ring or septal abscesses, while arteritis can be associated with mycotic aneurysms, ruptured aneurysms, or vertebral osteomyelitis.

Unlike most nontyphoidal *Salmonella* serotypes, *S. choleraesuis* and *S. dublin* are frequently associated with sustained bacteremia and fever, often in the absence of a history of gastroenteritis. Similarly, these serotypes appear to be especially invasive and are often associated with metastatic infection.

**Localized Infections**

*Intraabdominal Infections* Intraabdominal infections due to nontyphoidal *Salmonella* are rare and usually manifest as hepatic or splenic abscesses or as cholecystitis. Involvement of the pancreas and adrenals and even an infected pheochromocytoma have been reported. Risk factors include anatomic abnormalities of the hepatobiliary system, including gallstones; abdominal malignancy; and sickle cell disease (especially with splenic abscesses). Eradication of the infection often requires surgical correction of anatomic abnormalities and drainage of abscesses.

*Central Nervous System Infections Salmonella* infections of the central nervous system usually manifest as meningitis, although cerebral abscesses have been found.

Meningitis is usually seen in neonates (<4 months old) and is associated with severe sequelae, including residual seizures, hydrocephalus, ventriculitis, abscess formation, subdural empyema, and permanent disability (e.g., mental retardation and paralysis).

*Pulmonary Infections* Nontyphoidal *Salmonella* pulmonary infections usually present as lobar pneumonia, sometimes complicated by lung abscesses, empyemas, pleural effusions, and bronchopleural fistulas. The majority of cases occur in patients with a preexisting abnormality of lung or pleura, including malignancy. Additional risk factors include sickle cell disease and glucocorticoid use. It is important to determine whether the pulmonary infection is in fact due to *Salmonella* or whether it is a secondary infection.

*Urinary and Genital Tract Infections* Urinary tract infections caused by nontyphoidal salmonellae present as either cystitis or pyelonephritis, usually in association with malignancy, urolithiasis, structural abnormalities, or immunosuppression (HIV infection, renal transplantation). Genital infections due to these bacteria are rare and present as ovarian and testicular abscesses, prostatitis, or epididymitis. Like other focal infections, both genital and urinary tract infections can be complicated by abscess formation.

*Bone, Joint, and Soft Tissue Infections Salmonella* osteomyelitis most commonly affects the femur, tibia, humerus, or lumbar vertebrae and is most often seen in association with sickle cell disease, hemoglobinopathies, or preexisting bone disease (e.g., fractures). Prolonged antibiotic treatment is recommended to decrease the incidence of relapse and chronic osteomyelitis. Septic arthritis occurs in the same patient population as osteomyelitis and usually presents in the knee, hip, or shoulder joints. Reactive arthritis (Reiter's syndrome) can follow *Salmonella* gastroenteritis and is seen most frequently in persons with the HLA-B27 histocompatibility antigen. *Salmonella* can cause rare soft tissue infections, usually at sites of local trauma in immunosuppressed patients.

## DIAGNOSIS

Nontyphoidal *Salmonella* gastroenteritis is diagnosed when *Salmonella* is cultured from stool. All salmonellae isolated in clinical laboratories should be sent to local public health departments. In cases where there is concern about bacteremia (i.e., those including prolonged or recurrent fever), blood cultures are indicated. Once bacteremia is documented, it is important to determine whether it is high-grade (>50% of three or more blood cultures positive); if so, endovascular infection is possible and further evaluation to identify the source is indicated. In addition, depending on clinical symptoms and on whether metastatic disease is suspected, other body fluids, such as joint fluid or cerebrospinal fluid, should be cultured.

## TREATMENT

Antibiotic treatment is not generally recommended for *Salmonella* gastroenteritis. The symptoms are usually self-limited and have not been demonstrated to be altered by short courses of antibiotics. In addition, in case-control and double-blind placebo-controlled trials, antibiotic treatment has been associated with increased rates of relapse and prolonged gastrointestinal carriage. Dehydration secondary to diarrhea

should be treated with fluid and electrolyte replacement.

However, preemptive antibiotic treatment should be considered in patients at increased risk for metastatic infection. These patients include neonates (probably up to 3 months of age); persons >50 years old (because of the high risk of atherosclerotic plaque or aneurysm); transplant recipients; and patients with lymphoproliferative disease, HIV infection, prosthetic joints, vascular grafts, significant joint disease, or underlying sickle cell disease. This group should receive a course of oral or intravenous antibiotics lasting for 2 or 3 days or until defervescence. Longer courses of antibiotics are not recommended because they have been associated with higher rates of chronic carriage and relapse. Rare cases of chronic nontyphoidal *Salmonella* carriage should be treated with a prolonged antibiotic course, as described above for chronic carriage of *S. typhi*.

Focal infections or life-threatening bacteremia with nontyphoidal *Salmonella* should be treated with antibiotics (at the same doses used for enteric fever). Given the increasing prevalence of antibiotic resistance, empirical therapy should include a third-generation cephalosporin and/or a quinolone. If the bacteremia is low-grade (<50% of blood cultures positive), the patient should be treated for 7 to 14 days. Patients with AIDS and *Salmonella* bacteremia should receive 1 to 2 weeks of intravenous antibiotic therapy followed by 4 weeks of oral therapy with quinolones. Patients who relapse after this regimen should receive long-term suppressive therapy with a quinolone orTMP-SMZ, as indicated by bacterial sensitivities.

If the patient has an endovascular infection or endocarditis, treatment for 6 weeks with intravenous b-lactam antibiotics is indicated. Chloramphenicol treatment has been associated with high failure rates and is not recommended. Limited case reports have described the successful treatment of *Salmonella* endovascular infections with quinolones, which may prove an alternative approach in cases caused by sensitive strains. However, concern remains about the development of quinolone resistance during prolonged therapy. Surgical resection of infected aneurysms or other infected endovascular sites is often required. If surgical resection is not possible, lifelong suppressive antibiotic therapy may be indicated. For extraintestinal nonvascular infections, 2 to 4 weeks of antibiotic therapy (depending on the site) are usually recommended. In cases of chronic osteomyelitis, abscesses, and urinary or biliary tract abnormality, surgical interventions may be required in addition to prolonged antibiotic therapy to eradicate infection.

## PREVENTION AND CONTROL

The incidence of nontyphoidal salmonellosis continues to rise along with rates of emergence of antibiotic-resistant strains. The increased centralization of food production plays a prominent role in the growing incidence, as one oversight can result in rapid, widespread distribution of contaminated food. Thus, it is important to monitor every step of food production, from handling of raw products to preparation of finished foods. In particular, with the increasing prevalence of *S. enteritidis* in egg-laying hens, it is recommended that pasteurized eggs be substituted for bulk-pooled eggs at all nursing homes, hospitals, and commercial food-service establishments. All cases of nontyphoidal salmonellosis should be reported to public health departments, since tracking and monitoring of these cases result in the identification of the sources of local

outbreaks and help authorities anticipate large-scale international outbreaks. Lastly, the prudent use of antimicrobial agents in both humans and animals is necessary to minimize the further emergence of antibiotic-resistant strains.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 157. SHIGELLOSIS - *Gerald T. Keusch*

### DEFINITION

*Shigellosis* is an acute infectious inflammatory colitis due to one of the members of the genus *Shigella*. Although the disease is often referred to as "bacillary dysentery," many patients have only mild watery diarrhea and never develop dysenteric symptoms. Less severe illness predominates in industrialized countries such as the United States, whereas more severe, often fatal dysentery occurs in patients in developing countries.

### ETIOLOGIC AGENT

Shigellae are slender, gram-negative, nonmotile bacilli and are members of the family Enterobacteriaceae and the tribe Escherichieae. They are so closely related to *Escherichia coli* that the two genera cannot be distinguished by DNA hybridization methods. In fact, *Shigella* can be thought of as a differentiated pathogenic *E. coli*. The four *Shigella* species (*S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*) are defined on the basis of surface somatic O antigens and carbohydrate fermentation patterns. Most are lactose-negative (*S. sonnei* is a late lactose fermenter) and produce acid but not gas from glucose, resulting in a typical acid butt and alkaline slant in triple sugar iron agar without $H_2S$ production. The genus is characterized by its ability to invade intestinal epithelial cells and to cause infection and illness in humans, even when the inoculum is small (a few hundred to a few thousand organisms).

### EPIDEMIOLOGY

Worldwide, it is estimated that at least 140 million cases of shigellosis and almost 600,000 deaths due to shigellosis occur annually among children under the age of 5 years, primarily in developing countries. The organism is found everywhere in the world but is most common where poor environmental sanitation and crowding facilitate transmission from person to person. A major outbreak took place in the makeshift camps for refugees fleeing the Rwandan civil war in 1994, with thousands of cases and high mortality.

Data collected by the Centers for Disease Control and Prevention in the United States from 1967 through 1988 suggest an average annual incidence of 6 *Shigella* infections per 100,000 population, with periodic hyperendemic increases (primarily due to large outbreaks of *S. sonnei* infection) raising the rate to between 9 and 10 per 100,000. On the basis of these data, the annual number of episodes of shigellosis in the United States is estimated at 25,000 to 30,000. Incidence rates approximate 27 per 100,000 among children 1 to 4 years of age but are only 2.6 per 100,000 among persons 20 years of age or older. Cases are detected most commonly in counties with a relatively high proportion of low-income minority-group residents, including African Americans, Hispanics, and Native Americans; rates are especially high in poor urban communities, in day-care centers, and among retarded children in custodial care.

A comparison with rates among rural Guatemalan Indian children during the same period puts this disease burden into perspective. A prospective surveillance study among 321 such children revealed an annual incidence of nearly 10,000 per 100,000.

Since the description of the genus *Shigella*, major global shifts in the prevalence of its four species have been noted. Until World War I, *S. dysenteriae* type 1 was the predominant isolate, frequently causing devastating epidemics with high mortality until it was replaced by *S. flexneri*. Since World War II, however, *S. flexneri* has been steadily replaced by *S. sonnei* in the industrialized countries. The reasons for these shifts are not clear. *S. boydii*, the fourth species, has remained largely confined to the Indian subcontinent.

*Shigella* is highly host-adapted and is a natural pathogen only of humans and a few other primates. Transmission from person to person takes place by the fecal-oral route, generally via direct contact but sometimes through contaminated vectors such as food, water, flies, and fomites. Contaminated imported parsley from Mexico was responsible for one multistate outbreak of *S. sonnei* diarrhea. The organism can even be transmitted during participation in recreational water sports in fecally contaminated pools or lakes and can spread rapidly among confined populations in close contact -- for example, in day-care centers, in institutions for the mentally retarded, on cruise ships, or among military personnel. *Shigella* can be transmitted by anal-oral sexual practices among gay men; these cases are almost always due to *S. flexneri*. Rates of *Shigella* infection among HIV-infected individuals greatly exceed those in the non-HIV-infected population (Chap. 309).

Shigellosis is associated with a high rate of secondary household transmission. As many as 40% of children and 20% of adults who are household contacts of a case (generally a preschool child) will develop *Shigella* infection; the infection is often symptomatic in children but asymptomatic in adults, who seem to have an acquired immunity. In contrast, epidemic disease affects all ages, with clusters of severe and fatal cases in the very young and the very old. Since 1969, epidemic *S. dysenteriae* type 1 has reappeared in Latin America, in the Indian subcontinent and elsewhere in Asia, and in central and southern Africa and has been associated with relatively high mortality rates due to antimicrobial resistance and inadequate diagnosis and case management. Prolonged asymptomatic carriage is uncommon; unless there is underlying malnutrition, the organisms are generally cleared in a few weeks.

## PATHOGENESIS AND PATHOLOGY

Shigellae are orally ingested and, because they survive low pH more easily than other enteric pathogens (a genetically regulated property), seem to have little difficulty in passing the gastric acid barrier. An essential step in pathogenesis is invasion of colonic epithelial cells and cell-to-cell spread of infection. This step involves initial attachment of the organism to colonic cells, entry by an endocytic mechanism in which organisms are initially encased in and then escape from plasma membrane-enclosed vesicles, and a jet propulsion-like movement to the cell membrane, from which the organism can invade the adjacent cell. This sequence of events not only provides the organism with a means to evade host defenses but also allows its effective local spread. Although invasion is initially innocuous, subsequent intracellular multiplication causes cell damage and death, ultimately resulting in characteristic mucosal ulcerations.

These events are extremely complicated and require the functions of multiple genes and

regulatory elements encoded on both the chromosome and a large 120- to 140-MDa plasmid present in all virulent shigellae as well as enteroinvasive *E. coli* (EIEC), which can cause a *Shigella*-like disease. The number of structural and regulatory genes known to be involved in pathogenesis continues to increase as the process continues to be dissected. Some of these gene products induce the phagocytosis-like uptake of the organism by causing rearrangements of the host cell's cytoskeleton. Once a single *Shigella* organism has invaded a single host cell, the entire process of bacterial escape from the phagocytic vesicle into the host cell's cytoplasm, multiplication, and cell-to-cell spread can take place without exposure of the bacterium to the extracellular milieu and to the host's defenses.

It was originally thought that shigellae invade the host across the intestinal epithelial cells; however, studies using cell culture or a rabbit-ileum in vivo model have suggested that the initial invasion may occur via the antigen-sampling M cell. The resulting limited penetration by organisms initiates an inflammatory response with neutrophil infiltration of the lamina propria, which alters the functional integrity of tight junctions between epithelial cells. These changes allow more organisms to breach the mucosal barrier at intercellular junctions and are essential for the development of illness. If neutrophil migration is directly inhibited by the treatment of animals with antibody to CD18, the escalating invasion by microorganisms does not take place.

Escape from the phagocytic vesicle is necessary for the virulence of shigellae and permits multiplication of the organisms in the cytoplasm. The multiplying organisms spread within the cytoplasm to the plasma membrane of the host cell and then from cell to cell. This spread is achieved by the polymerization of actin at the back end of the dividing bacteria (defined relative to the subsequent direction of motion). Binding and cross-linking by the host protein plastin result in a sphincter-like contraction that provides a forward propulsive force. This so-called actin motor is energized by ATP generated by a microbial-encoded ATPase called *IcsA*, which is, at the same time, phosphorylated and regulated by cyclic nucleotide-dependent protein kinases of the host. Phosphorylation may serve as a molecular host-defense mechanism to modulate virulence, limiting microbial spread.

Another important host protein involved in pathogenesis of shigellosis is the cadherin L-CAM, which is essential in the cell-to-cell spread of infection. Mutations in L-CAM alter the long finger-like protrusions induced by shigellae when they reach the plasma membrane and impair their subsequent fusion with the plasma membrane of the adjacent cell, thus inhibiting the transfer of the bacterium from one cell to another. Ultimately, the invaded host cell dies, possibly as a result of apoptosis induced by or during the process of microbial invasion.

Another property of apparent importance in virulence for *S. dysenteriae* type 1 is the ability to produce Shiga toxin, which is encoded by the iron-regulated chromosomal gene *stx*. Shiga toxin is composed of two distinct peptide subunits, each with highly conserved active regions. The first, located on the larger A subunit, is an *N*-glycosidase that hydrolyzes adenine from specific sites of ribosomal RNA of the mammalian 60S ribosomal subunit, irreversibly inhibiting protein synthesis. The second common region is a binding site on the B subunit that recognizes glycolipids of target cell membranes that terminate in a galactosea1 ® 4-galactose disaccharide. The glycolipid Gb3,

containing a gal-gal-glu trisaccharide, is a specific receptor present on toxin-sensitive rabbit intestinal villus cells but not crypt cells, and toxin action is specific for the former.

Wild-type toxigenic *S. dysenteriae* causes more severe illness in primates than does an isogenic toxin-negative mutant. The toxin of this organism, the prototype of a family of related toxin proteins produced by enterohemorrhagic *E. coli* (EHEC), appears to play a role in the pathogenesis of microangiopathic complications, hemolytic-uremic syndrome (HUS), and thrombotic thrombocytopenic purpura: only toxin-producing shigellae and *E. coli* are associated with these systemic illnesses. Two new *Shigella* enterotoxins, ShET-1 and -2, have been described; the former is restricted almost exclusively to *S. flexneri* 2a, whereas the latter is distributed more widely (e.g., in the physiologically similarEIEC). The two enterotoxins are encoded by chromosomal and plasmid genes, respectively. Both toxins alter electrolyte transport by segments of gut in vitro and cause net fluid secretion in vivo in ligated rabbit ileal loops. Moreover, both toxins induce antibody in infected humans. However, their role (if any) in the pathogenesis of the watery diarrhea phase of shigellosis remains uncertain.

In shigellosis, the epithelial surface of the human colon shows extensive ulcerations, with an exudate consisting of desquamated colonic cells, polymorphonuclear leukocytes, and erythrocytes; the ulcerations may resemble a pseudomembrane in severely affected areas. Marked mucus depletion and increased mitotic activity are evident in the crypt regions and presumably reflect a response to the loss of surface colonic cells. The lamina propria is edematous and hemorrhagic and is infiltrated by neutrophils and plasma cells. There is also swelling of capillary and venular endothelial cells, with margination of neutrophils. At the ultrastructural level, bacteria can be seen within vesicles as well as free in the cytoplasm. Histologic examination of colon from dysenteric humans shows an alteration of mucosal endothelial cells similar to that induced by endotoxin [lipopolysaccharide (LPS)]. Shiga toxin (protein) targets endothelial cells as well, especially when toxin receptor expression is upregulated by exposure to LPS or proinflammatory cytokines. Levels of circulating LPS are high in *S. dysenteriae* type 1 infection and somewhat lower in *S. flexneri* infection, even without bacteremia. The frequency of endotoxemia in shigellosis suggests a broader role for LPS in the pathogenesis of the disease. One likely mechanism is related to the ability of LPS to induce cytokine gene transcription and the strong association of cytokine secretion and inflammation. However, bacterial invasion of the mucosa itself activates the transcription factor NF-kB, which is involved in regulation of cytokine synthesis. Cytokine-producing cells are present in the mucosa of patients infected with *S. dysenteriae* or *S. flexneri* and in their stools as well. In fact, the number of cells producing interleukin 1, interleukin 6, interferon a, and transforming growth factorb is directly related to the severity of the inflammation. Inflammatory changes in *Shigella* infection thus appear to be components of the pathogenesis of dysentery as much as they are a consequence of the bacterial invasive process.

Epidemiologic evidence indicates that immunity develops and is serotype-specific. The precise nature of this immunity is not known. Common surface outer-membrane proteins involved in invasion elicit serum antibodies; although these are cross-reactive among *Shigella* species and serotypes, they do not seem to be protective. The serotype-specific determinants are likely to be somatic antigens, as serum antibody toLPSpredicts resistance to infection, and there is evidence of IgA-mediated mucosal

responses to LPS during convalescence from shigellosis.

## CLINICAL MANIFESTATIONS

Shigellosis in the United States, due primarily to *S. sonnei*, is typically an ambulatory disease, presenting as a self-limited nonbloody watery diarrhea chock full of neutrophils. The spectrum of clinical shigellosis was shown in a study in which adult volunteers ingested 10,000 organisms of *S. flexneri* type 2a. While approximately one-quarter of the volunteers never became ill, over the first 24 to 48 h ~25% developed transient fever, another 25% had fever and self-limited watery diarrhea, and the remaining 25% had fever and watery diarrhea that progressed to bloody diarrhea and dysentery. In young children in particular, the temperature can rise rapidly to 40° to 41°C and sometimes results in generalized seizures. These seizures rarely recur or result in serious sequelae. Dysentery is characterized by frequent passage (usually 10 to 30 times per day) of small-volume stools consisting of blood, mucus, and pus; this diarrhea is accompanied by abdominal cramps and tenesmus -- the painful straining with stooling that may lead to rectal prolapse, especially in young children. Severe dysentery is most likely in infection due to *S. dysenteriae* type 1, occurs less commonly with *S. flexneri*, and is least likely in *S. sonnei* infection. Patients with mild disease generally recover without specific therapy in a few days to a week. Severe shigellosis can progress to toxic dilatation and colonic perforation, which may be fatal.

Endoscopy shows the mucosa to be hemorrhagic, with mucous discharge and focal ulcerations and sometimes with overlying exudate. The majority of lesions are in the distal colon and progressively diminish in the more proximal segments of large bowel. Mild dehydration is common among patients with watery diarrhea; severe dehydration is very rare. With extensive colonic involvement, protein-losing enteropathy can occur and can have important adverse nutritional consequences, especially for already poorly nourished children.

A variety of *extraintestinal complications* of shigellosis have been described. The majority arise in patients in developing countries and are related both to the prevalence of infections due to *S. dysenteriae* type 1 and *S. flexneri* and to the poor nutritional state of the host. For example, bacteremia, thought to be relatively infrequent in the United States, develops in up to 8% of patients hospitalized for shigellosis in Dacca, Bangladesh. The causative *Shigella* species is isolated from half the patients; other Enterobacteriaceae are found in the remainder. Bacteremia is associated with higher-than-usual mortality and is more common among infants<1 year of age and among persons with protein-energy malnutrition. Persistent and clinically severe *Shigella* bacteremia has been encountered in the United States in patients with AIDS (Chap. 309).

HUSmay occur with *S. dysenteriae* type 1 infection. In the United States, the more likely cause of HUS is one of the hemorrhagic colitis-causing strains of *E. coli* (such as *E. coli* O157:H7) that produce high levels of Shiga-family toxins. HUS usually develops toward the end of the first week of shigellosis, when dysentery is already resolving. Oliguria and a marked drop in hematocrit (by as much as 10% within 24 h) are the first signs and may progress to anuria with renal failure and to severe anemia with congestive heart failure, respectively. Even with advanced therapy, 5 to 10% of patients with HUS die of

the acute illness. In addition, renal damage progresses slowly over several decades in survivors, an estimated 50% of whom develop significant renal failure and most of whom require long-term dialysis or renal transplantation. Leukemoid reactions, with leukocyte counts of >50,000/uL, may occur along with HUS; thrombocytopenia (with 30,000 to 100,000 platelets/uL) is common. Profound hyponatremia and severe hypoglycemia may be documented. Central nervous system abnormalities include encephalopathic symptoms, seizures, altered consciousness, and bizarre posturing.

Less common extraintestinal manifestations include seizures in some patients and reactive arthritis in others; both of these manifestations are usually due to infection with *S. flexneri* strains. In patients expressing histocompatibility antigen HLA-B27, the full triad of Reiter's syndrome sometimes develops (Chap. 315). Pneumonia, meningitis, vaginitis (in prepubertal girls), keratoconjunctivitis, and "rose spot" rashes are rare events.

## DIAGNOSIS AND LABORATORY FINDINGS

Shigellosis is the principal bacterial cause of dysentery and should be considered whenever a patient presents with bloody diarrhea. However, in the United States, because *S. sonnei* is the most common species, most patients present with fever and nonbloody watery diarrhea indistinguishable from signs caused by other bacterial or viral agents of mild to moderate diarrhea, while many patients with bloody diarrhea haveEHEC as the cause. The specific diagnosis is based on culture of *Shigella* from the stool; however, diagnosis by the polymerase chain reaction is possible, and a commercial enzyme immunoassay to detect Shiga-family toxins in stool can identify most patients infected with *S. dysenteriae* type 1 or EHEC within 3 h. The yield of *Shigella* is increased if the organism is sought by stool culture when the patient has fecal leukocytes or bloody diarrhea. The organism is very labile and must be transferred quickly to plates or holding media (such as buffered glycerol saline) if it is to survive. Stool samples are preferable to swabs; when the latter are used, a rectal sample should be obtained. More than one selective medium should be used for culture -- i.e., MacConkey and one other, such as Hektoen enteric or xylose-lysine-deoxycholate. Stool cultures to diagnose nonbloody watery diarrhea have a very low yield of positives and are not cost-effective.

Serologic tests can be performed, since antibodies to somatic antigens develop early in the acute phase of disease. However, the resources for such tests are not generally available, and serologic assessments usually are used only for epidemiologic studies.

The differential diagnosis includes inflammatory colitis due to other microbial agents:EHEC,EIEC, *Campylobacter jejuni*, *Salmonella enteritidis*, *Yersinia enterocolitica*, *Clostridium difficile*, and the protozoan *Entamoeba histolytica*. Ulcerative colitis and Crohn's colitis are among the "noninfectious" conditions that should be considered (Chap. 287). All these infections except that due to *E. histolytica* are associated with the presence of large numbers of fecal leukocytes. Amebiasis can be diagnosed by the detection of erythrophagocytic trophozoites in the stool (Chap. 213).

Other laboratory studies are nonspecific and may disclose neutrophilic leukocytosis, anemia due to blood loss with hemorrhagic diarrhea, prerenal azotemia, or (if watery

diarrhea has been pronounced) hyperchloremic acidosis. Laboratory findings in shigellosis complicated byHUS are discussed above.

**TREATMENT**

The mild to moderate dehydration in shigellosis is readily corrected with oral rehydration solutions (Chap. 159). The role of antibiotic therapy is variable and depends on the organism and the severity of disease. Since *S. sonnei* infection is usually self-limited, culture results generally do not become available until the patient is better and there is little clinical need for further therapy. The use of antibiotics in severe cases with bloody diarrhea or dysentery reduces the duration of illness and can shorten the carriage state. Resistance to sulfonamides, streptomycin, chloramphenicol, and tetracyclines is almost universal, and many shigellae are now resistant to ampicillin and trimethoprim-sulfamethoxazole as well. Knowledge of the pattern of resistance in a given population, which can change with time, is useful. In the United States, multiresistant strains are most likely to be acquired during travel abroad; either ampicillin (50 to 100 mg/kg per day in children or 2 g/d in adults, in divided doses) or trimethoprim-sulfamethoxazole (8/40 mg/kg per day in children or 2 regular-strength tablets twice a day in adults, given for 5 days) is generally recommended for domestically acquired infection. Short courses of treatment (1 or 3 days) or even single doses of drugs like tetracycline and ciprofloxacin have been employed with success and may soon become the standard. Amoxicillin should *not* be substituted for ampicillin because it is not effective against shigellosis. In developing countries, where resistance to both of these drugs is commonplace, the drug of choice for the treatment of multiresistant *S. dysenteriae* type 1 infections has been nalidixic acid (55 mg/kg per day for 5 days); however, resistance to the latter agent is increasing in prevalence. The 4-fluoroquinolones (e.g., ciprofloxacin) are highly effective against all strains (Chap. 137) but are currently too costly in the developing world and are not yet approved for use in children under 17 in the United States; these drugs have caused cartilage damage in young rodents during toxicity tests, although there is no evidence for a similar effect of therapeutic doses in humans. Alternative drugs shown to be effective include oral pivamdinocillin (amdinocillin, pivoxil, pivmecillinam; still not available in the United States), azithromycin, and intravenous ceftriaxone (50 mg/kg per day for 5 days). In small-scale clinical trials, cephalexin has had no effect in limiting symptoms; single doses of ceftriaxone may be effective, but more information is needed. No antibiotic treatment is recommended for the convalescent carrier state, which usually lasts no more than several weeks. Patients with AIDS may develop chronic carriage of *Shigella* and may be subject to relapsing infection with bacteremia (Chap. 309). This cycle may be interrupted by prolonged (several weeks') treatment with a quinolone.

The role of antimotility agents such as atropine sulfate and diphenoxylate (Lomotil) and loperamide (Imodium) in the early phases of shigellosis is controversial. Loperamide, in particular, may reduce diarrhea and in one study was highly effective in combination with antimicrobials. However, these antimotility drugs are suspected of enhancing the severity of disease by delaying excretion of organisms and thus facilitating further invasion of the mucosa and complicating toxic megacolon. Therefore, they are contraindicated in infants and young children. In adults, these agents are contraindicated for use in the dysenteric phase of disease.

Treatment of complications of shigellosis often differs in developed and developing countries. For example, antibiotic-unresponsive toxic megacolon, with or without perforation, is often managed by colectomy in the United States. Surgery is less often employed in developing countries because of a lack of availability or difficulties in ileostomy management.HUSoften requires dialysis. In developing countries, dialysis may be needed relatively infrequently because azotemia is slow to develop and the risk of significant hyperkalemia is often diminished by a preexisting deficiency in total-body potassium, with malnutrition and wasting of lean body mass. The management of hyponatremia, usually caused by inappropriate secretion of antidiuretic hormone (vasopressin), is governed by the severity of the condition and the symptomatic state of the patient, as outlined inChap. 49. Infusion of glucose can reverse clinical manifestations caused by hypoglycemia, and responses can be monitored by finger-stick blood glucose tests if no biochemistry laboratory is available. Optimal nutritional management is needed to correct deficiencies due to underlying malnutrition as well as the superimposed catabolic stress and protein-losing enteropathy of shigellosis. Nutritional support should begin during the acute illness and may be required for months thereafter (Chap. 76).

**PREVENTION**

Direct-contact transmission of shigellosis can be prevented by appropriate environmental and personal hygiene. Hand washing with soap and water, decontamination of water supplies, use of sanitary latrines or toilets, and precautions in the preparation and storage of food can all reduce the primary and secondary transmission of *Shigella* infection. In highly endemic developing countries, infants are protected during the period of exclusive breast feeding, which should be encouraged. Any measures that reduce the burden of malnutrition will also reduce the burden of shigellosis in the population. Stool precautions should be instituted for hospitalized infected patients to ensure safe disposal of infected excreta and linens, and hospital personnel must wash their hands and medical instruments (such as stethoscopes) after each contact with an infected patient. Cohorting of asymptomatic infected children, use of antibiotics to reduce infectiousness, and scrupulous attention to hygiene are usually successful in nosocomial outbreaks. Children in day care must be kept at home while clinically ill and ideally should have a negative stool culture before returning to the day-care facility. Likewise, food handlers who develop shigellosis should be culture-negative before returning to work. Antibiotic treatment is not indicated for the asymptomatic carrier state. No effective vaccine is available, although promising initial results have been reported with an *S. sonnei*LPS-protein conjugate vaccine.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 158. INFECTIONS DUE TO *CAMPYLOBACTER* AND RELATED SPECIES - *Martin J. Blaser*

### DEFINITION

Bacteria of the genus *Campylobacter* and of the related genera *Arcobacter* and *Helicobacter* (Chap. 154) cause a variety of pyogenic infections. Although acute diarrheal illnesses are most common, these organisms may cause infections in virtually all parts of the body, especially in compromised hosts, and these infections may have late nonsuppurative sequelae. The designation *Campylobacter* comes from the Greek for "curved rod" and refers to the organism's vibrio-like morphology.

### ETIOLOGY

Campylobacters are motile, non-spore-forming, curved gram-negative rods. Originally known as *Vibrio fetus*, these bacilli were reclassified as a new genus in 1973, after it was recognized that they were quite dissimilar to other vibrios. Since then, more than 15 species have been identified. These species are currently divided into three genera: *Campylobacter*, *Arcobacter*, and *Helicobacter*. Not all of the species are pathogens of humans. The human pathogens can be divided into two major groups: those that primarily cause diarrheal disease and those that cause extraintestinal infection. The principal diarrheal pathogen is *C. jejuni*, which accounts for 80 to 90% of all cases of recognized illness due to campylobacters. Other organisms that cause diarrheal disease include *C. coli*, *C. upsaliensis*, *C. lari*, and *C. fetus*. The major species causing extraintestinal illnesses is *C. fetus*; however, any of the diarrheal agents may cause systemic or localized infection as well. Neither aerobes nor strict anaerobes, these microaerophilic organisms are adapted for survival in the gastrointestinal mucous layer. This chapter will focus on *C. jejuni* and *C. fetus* as the major pathogens and prototypes for their groups; the key features of infection are listed by species (excluding *C. jejuni*, described in detail in the text below) in Table 158-1.

### EPIDEMIOLOGY

Campylobacters are found in the gastrointestinal tract of many animals used for food (including poultry, cattle, sheep, and swine) and of many household pets (including birds, dogs, and cats). These microorganisms usually do not cause illness in their animal hosts. In most cases, campylobacters are transmitted to humans in raw or undercooked food products or through direct contact with infected animals. In the United States and other developed countries, ingestion of contaminated poultry that has not been sufficiently cooked is the most common means of acquiring infection (50 to 70% of cases). Other modes of transmission include ingestion of raw (unpasteurized) milk or untreated water, contact with infected household pets, travel to developing countries (campylobacters being among the causes of traveler's diarrhea; Chap. 131), and (occasionally) contact with an index case who is incontinent of stool.

*Campylobacter* infections are not rare. Several studies indicate that, in the United States, diarrheal disease due to campylobacters is more common than that due to *Salmonella* and *Shigella* combined. Infections occur throughout the year, but their incidence peaks during summer and early autumn. Persons of all ages are affected;

however, attack rates for *C. jejuni* are highest among young children and young adults, while those for *C. fetus* are highest at the extremes of age. Systemic infections due to *C. fetus* (and to other *Campylobacter* and related species) are most common in compromised hosts. Persons at increased risk include those with AIDS, hypogammaglobulinemia, neoplasia, liver disease, diabetes mellitus, and generalized atherosclerosis as well as pregnant women. However, apparently healthy nonpregnant persons occasionally develop transient *Campylobacter* bacteremia as part of a gastrointestinal illness.

In developing countries, *C. jejuni* infections are hyperendemic, with the highest rates among children <2 years old. Infection rates fall with age, as does the illness-to-infection ratio; these observations suggest that frequent exposure to *C. jejuni* leads to the acquisition of immunity.

## PATHOLOGY AND PATHOGENESIS

Many *C. jejuni* infections are subclinical, especially in partially immune hosts. Most illnesses occur within 2 to 4 days (range, 1 to 7 days) of exposure to the organism in food or water. The sites of tissue injury include the jejunum, ileum, and colon. Biopsies show an acute nonspecific inflammatory reaction, with neutrophils, monocytes, and eosinophils in the lamina propria, as well as damage to the epithelium, including loss of mucus, glandular degeneration, and crypt abscesses. Biopsy findings may be consistent with Crohn's disease or ulcerative colitis, but these "idiopathic" chronic inflammatory diseases should not be diagnosed unless infectious colitis, *specifically including* that due to infection with *Campylobacter*, has been ruled out.

The high frequency of *C. jejuni* infections and their severity and recurrence among hypogammaglobulinemic patients suggest that antibodies are important in protective immunity. The pathogenesis of infection is uncertain. Both the motility of the strain and its capacity to adhere to host tissues appear to favor disease, but classic enterotoxins and cytotoxins (although described) appear not to play any substantial role in tissue injury or disease production. The organisms have been visualized in the epithelium, albeit in low numbers. The documentation of a significant tissue response and occasionally of *C. jejuni* bacteremia further suggests that tissue invasion is clinically significant.

The pathogenesis of *C. fetus* infections is better defined. Virtually all clinical isolates of *C. fetus* possess a proteinaceous capsule-like structure (an S-layer) that renders the organism resistant to complement-mediated killing and opsonization. As a result, *C. fetus* can cause bacteremia and can seed sites beyond the intestinal tract. The ability of the organism to switch the S-layer proteins expressed, a phenomenon that results in antigenic variability, may contribute to the chronicity and high rate of recurrence of these infections in compromised hosts.

## CLINICAL MANIFESTATIONS OF *C. JEJUNI* AND *C. FETUS* INFECTIONS

The clinical features of infections due to all of the *Campylobacter* and related species causing enteric disease appear to be highly similar. There is often a prodrome, with fever, headache, myalgia, and/or malaise, 12 to 48 h before the onset of diarrheal

symptoms. The most common symptoms of the intestinal phase are diarrhea, abdominal pain, and fever. The degree of diarrhea varies from several loose stools to grossly bloody stools; most patients presenting for medical attention have 10 or more bowel movements on the worst day of illness. Abdominal pain usually consists of cramping and may be the most prominent symptom. Pain usually is generalized but may become localized; *C. jejuni* infection may cause pseudoappendicitis. Fever may be the only initial manifestation of *C. jejuni* infection, a situation mimicking the early stages of typhoid fever. Febrile young children may develop convulsions. *Campylobacter* enteritis generally is self-limited; however, symptoms persist for longer than 1 week in 10 to 20% of patients seeking medical attention, and relapses occur in 5 to 10% of untreated patients.

*C. fetus* may cause a diarrheal illness similar to that due to *C. jejuni*, especially in normal hosts, or may cause either intermittent diarrhea or nonspecific abdominal pain without localizing signs. Sequelae are uncommon, and outcome is benign. *C. fetus* also may cause a prolonged relapsing systemic illness (with fever, chills, and myalgias) that has no obvious primary source; this manifestation is especially common in compromised hosts. Secondary seeding of an organ (e.g., meninges, brain, bone, urinary tract, or soft tissue) complicates the course, which may be fulminant. *C. fetus* infections have a tropism for vascular sites: endocarditis, mycotic aneurysm, and septic thrombophlebitis all may occur. Infection during pregnancy often leads to fetal death. *H. cinaedi* causes recurrent cellulitis with fever and bacteremia in immunocompromised hosts.

## COMPLICATIONS

Except in the case of infection with *C. fetus*, bacteremia is uncommon, developing most often in immunocompromised hosts and at the extremes of age. Three patterns of extraintestinal infection have been noted: (1) transient bacteremia in a normal host with enteritis (benign course, no specific treatment needed); (2) sustained bacteremia or focal infection in a normal host (bacteremia originating from enteritis, with patients responding well to antimicrobial therapy); and (3) sustained bacteremia or focal infection in a compromised host. Enteritis may not be clinically apparent. Antimicrobial therapy, possibly prolonged, is necessary for suppression or cure of the infection.

*Campylobacter* infections in patients with AIDS or hypogamma-globulinemia may be severe, persistent, and extraintestinal; relapse after cessation of therapy is common. Hypogammaglobulinemic patients also may develop osteomyelitis and an erysipelas-like rash.

Local suppurative complications of infection include cholecystitis, pancreatitis, and cystitis; distant complications include meningitis, endocarditis, arthritis, peritonitis, cellulitis, and septic abortion. All are rare. Hepatitis, interstitial nephritis, and the hemolytic-uremic syndrome occasionally complicate acute infection. Reactive arthritis and other rheumatologic complaints may develop several weeks after infection, especially in persons with the HLA-B27 phenotype. Guillain-Barre syndrome follows *Campylobacter* infections uncommonly (i.e., in 1 of every 1000 to 2000 cases). For certain *C. jejuni* serotypes, such as O19, Guillain-Barre syndrome may follow 1 in every 100 to 200 cases. Because of their high incidence, it is now estimated that

*Campylobacter* infections may trigger 20 to 40% of all cases of Guillain-Barre syndrome.

## LABORATORY FINDINGS

In patients with *Campylobacter* enteritis, peripheral leukocyte counts reflect the severity of the inflammatory process. However, stools from nearly all *Campylobacter*-infected patients presenting for medical attention in the United States contain leukocytes or erythrocytes. Fecal smears should be treated with Gram's or Wright's stain and examined in all suspected cases. When the diagnosis of *Campylobacter* enteritis is suspected on the basis of findings indicating inflammatory diarrhea (fever, fecal leukocytes), clinicians can ask the laboratory to attempt the visualization of organisms with characteristic vibrioid morphology by direct microscopic examination of stools with Gram's staining or to use phase-contrast or dark-field microscopy to identify the organisms' characteristic "darting" motility. Confirmation of the diagnosis of *Campylobacter* infection is based on identification of an isolate from cultures of stool, blood, or another site. *Campylobacter*-specific media should be used to culture stools from all patients with inflammatory or bloody diarrhea. Since all *Campylobacter* species are fastidious, they will not be isolated unless selective media or other selective techniques are used. Not all media are equally useful for isolation of the broad array of campylobacters; therefore, failure to isolate campylobacters from stool does not entirely rule out their presence. The detection of the organisms in stool almost always implies infection; there is a brief period of postconvalescent fecal carriage and no commensalism in humans. In contrast, *C. sputorum* and related organisms found in the oral cavity are commensals with rare pathogenic significance.

## DIFFERENTIAL DIAGNOSIS

The symptoms of *Campylobacter* enteritis are not sufficiently unusual to distinguish this illness from that due to *Salmonella*, *Shigella*, or *Yersinia*, among other pathogens. The combination of fever and fecal leukocytes or erythrocytes is indicative of inflammatory diarrhea, and definitive diagnosis is based on culture or demonstration of the characteristic organisms on stained fecal smears. Similarly, extraintestinal *Campylobacter* illness is diagnosed by culture. Infection due to *Campylobacter* should be suspected in the setting of septic abortion and that due to *C. fetus* specifically in the setting of septic thrombophlebitis. It is important to reiterate that the presentation of *Campylobacter* enteritis may mimic that of ulcerative colitis or Crohn's disease, that *Campylobacter* enteritis is much more common than either of the latter (especially among young adults), and that biopsy may not distinguish among these entities. Thus a diagnosis of inflammatory bowel disease should not be made until *Campylobacter* infection has been ruled out, especially in persons with a history of foreign travel, significant animal contact, immunodeficiency, or practices incurring a high risk of transmission.

## TREATMENT

Fluid and electrolyte replacement is central to the treatment of diarrheal illnesses (Chap. 131). Even among patients presenting for medical attention with *Campylobacter* enteritis, fewer than half will clearly benefit from specific antimicrobial therapy.

Indications for such therapy include high fever, bloody diarrhea, severe diarrhea, persistence for more than 1 week, and worsening of symptoms. A 5- to 7-day course of erythromycin (250 mg orally four times daily or -- for children -- 30 to 50 mg/kg per day, in divided doses) is the regimen of choice. Although no relevant clinical trials have been conducted, the in vitro susceptibility of *Campylobacter* species to macrolides such as clarithromycin and azithromycin suggests that these antibiotics also would be useful therapeutic agents. An alternative regimen for adults is ciprofloxacin (500 mg orally twice daily) or another fluoroquinolone for 5 to 7 days, but resistance to this class of agents is increasing. Other alternatives include tetracycline and furazolidone. Use of antimotility agents, which may prolong the duration of symptoms and has been associated with toxic megacolon and with death, is not recommended.

For systemic infections, treatment with gentamicin (1.7 mg/kg intravenously every 8 h after a loading dose of 2 mg/kg), imipenem (500 mg intravenously every 6 h), or chloramphenicol (50 mg/kg intravenously each day in three or four divided doses) should be started empirically, but susceptibility testing should then be performed. Ciprofloxacin and amoxicillin/clavulanate are alternative agents for susceptible strains. In the absence of immunocompromise or endovascular infections, therapy should be administered for 14 days. For immunocompromised patients with systemic infections due to *C. fetus* and for patients with endovascular infections, prolonged therapy (for up to 4 weeks) is usually necessary.

**PROGNOSIS**

Nearly all patients recover fully from *Campylobacter* enteritis, either spontaneously or after antimicrobial therapy. Volume depletion likely contributes to the few deaths that are reported. As stated above, occasional patients develop reactive arthritis or Guillain-Barre syndrome. Systemic infection with *C. fetus* is much more often fatal than that due to related species; this higher mortality reflects in part the population affected. Prognosis is dependent on the rapidity with which appropriate therapy is begun. Otherwise healthy hosts usually survive *C. fetus* infections without sequelae. Compromised hosts often have recurrent infections.

(Bibliography omitted in Palm version)

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Back to Table of Contents

# 159. CHOLERA AND OTHER VIBRIOSES - *Gerald T. Keusch*, *Robert L. Deresiewicz*, *Matthew K. Waldor*

Members of the genus *Vibrio* cause a number of important infectious syndromes. Classic among them is cholera, a devastating diarrheal disease caused by *V. cholerae* that has been responsible for seven global pandemics and much suffering over the past two centuries. Epidemic cholera remains a major public health concern and is dealt with at length in this chapter. Other vibrioses have also been described, including syndromes of diarrhea, soft tissue infection, or primary sepsis caused by additional named species in the genus *Vibrio*. These, too, are considered below.

All members of the genus are highly motile, facultatively anaerobic, curved gram-negative rods with one or more polar flagella. Except for *V. cholerae* and *V. mimicus*, all require salt for growth ("halophilic vibrios"). In nature, vibrios most commonly reside in tidal rivers and bays under conditions of moderate salinity. They proliferate in the summer months when water temperatures exceed 20°C. As might be expected, the illnesses they cause also increase in frequency during the warm months.

## CHOLERA

### DEFINITION

Cholera is an acute diarrheal disease that can, in a matter of hours, result in profound, rapidly progressive dehydration and death. Accordingly, cholera gravis (the severe form of cholera) is a much-feared disease, particularly in its epidemic presentation. Fortunately, prompt aggressive fluid repletion and supportive care can obviate the high mortality that it has historically wrought. While the term *cholera* has occasionally been applied to any severely dehydrating secretory diarrheal illness, whether infectious in etiology or not, it has generally referred to disease caused by *V. cholerae* serogroup O1. In 1992, however, a new epidemic serogroup (O139) that causes epidemic cholera emerged on the Indian subcontinent and has since killed many thousands of people.

### ETIOLOGY AND EPIDEMIOLOGY

The species *V. cholerae* comprises a host of organisms classified on the basis of the carbohydrate determinants of their lipopolysaccharide (LPS) O antigens. Some 155 serogroups have now been recognized. They are divided into those that agglutinate in antisera to the O1 group antigen (*V. cholerae* O1) and those that do not (non-O1 *V. cholerae*). Although some non-O1 *V. cholerae* serogroups have occasionally caused sporadic outbreaks of diarrhea, serogroup O1 was, until the emergence of serogroup O139, the exclusive cause of epidemic cholera. *V. cholerae* O139 (also called *V. cholerae* Bengal) is discussed in greater detail below.

*V. cholerae* O1 exists in two biotypes, *classical* and *El Tor*, that are distinguished on the basis of a number of characteristics, including phage susceptibility and hemolysin production. Each biotype is further subdivided into two serotypes, termed *Inaba* and *Ogawa*. Serotyping is a useful tool in field epidemiologic studies. Newer molecular epidemiologic techniques, such as ribotyping and other gene-based methods, now make it possible to trace the source and origin of cholera strains from around the world.

The natural habitat of *V. cholerae* is coastal salt water and brackish estuaries, where the organism lives in close relation to plankton and where it may survive in a viable but nonculturable form. Humans become infected incidentally but, once infected, can act as vehicles for spread. Ingestion of water contaminated by human feces is the most common means of acquisition of *V. cholerae*. Consumption of contaminated food in the home, in restaurants, or from street vendors can also contribute to spread. There is no known animal reservoir. While the infectious dose is relatively high, it is markedly reduced in hypochlorhydric persons, in those using antacids, and when gastric acidity is buffered by a meal. Cholera is predominantly a pediatric disease in endemic areas, but it affects adults and children equally when newly introduced into a population. In endemic areas, the disease is more common in the summer and fall months. While this seasonality has not been explained fully, it may be due to environmental conditions that affect the multiplication of vibrios or to seasonal alterations in human behavior that affect contact with water. Asymptomatic infections are frequent and more common with the El Tor than the classical biotype. In endemic areas, children<2 years of age are less likely to develop severe cholera than are older children, perhaps because of passive immunity acquired from breast milk. For unexplained reasons, susceptibility to cholera is significantly influenced by ABO blood group status; those with type O blood are at greatest risk, while those with type AB are at least risk.

Cholera is native to the Ganges delta in the Indian subcontinent. Since 1817, seven global pandemics have occurred. The current (seventh) pandemic -- the first due to the El Tor biotype -- began in Indonesia in 1961 and spread throughout Asia as *V. cholerae* El Tor displaced the endemic classical strain in many areas. It briefly invaded Europe, but effective public health measures and the high level of sanitation combined to limit its impact. In the early 1970s, El Tor cholera exploded in Africa, causing major epidemics before becoming a persistent endemic problem. Its recent history in Africa has been punctuated by severe outbreaks, often fed by the chaos of war and genocide. Such was the case in the camps for Rwandan refugees set up in 1994 around Goma, Zaire. Tens of thousands of cases occurred and mortality was high. In 1995, the occurrence of hundreds of cases in Romania and the Black Sea states of the former Soviet Union demonstrated the potential of this organism to cause epidemics whenever public health measures break down.

Since 1973, sporadic endemic infections due to vibrios related to the seventh-pandemic strain have been recognized along the U.S. Gulf Coast of Louisiana and Texas. These infections are typically associated with the consumption of contaminated, locally harvested shellfish. Occasionally, cases in U.S. locations remote from the Gulf Coast have been linked to shipped-in Gulf Coast seafood.

Although the event was long expected, it was not until 1991 that the current cholera pandemic reached Latin America. Beginning along the Peruvian coast in January 1991, the disease was carried by fishermen to Ecuador and Colombia. It then spread in an explosive epidemic to virtually all of South and Central America and to Mexico (Fig. 159-1). About 400,000 cases were reported in the first year of the outbreak, and >1 million had been reported by the end of 1994. While the cumulative mortality rate has been<1%, the mortality rate approached 30% in the communities first affected, where a lack of familiarity with the disease led initially to the deployment of wholly ineffective

treatment. Intensive education of health care providers and of the community at large has enhanced awareness of the disease and its appropriate management and has greatly diminished mortality. As it did in Africa two decades earlier, the epidemic El Tor strain proved capable of establishing itself in inland waters rather than in its classic niche of coastal salt waters; the organism has already become endemic in many of the Latin American countries into which it was recently introduced.

Cases linked to the Latin American epidemic have occurred in the United States. For example, 11 people in New York and New Jersey were infected in two separate outbreaks in 1991 after eating boiled crabmeat illegally transported by travelers from Ecuador. Although secondary spread of this strain has not taken place in the United States, these events underscore the need for vigilance among health care professionals, even in locations remote from an epidemic.

In October 1992, a large-scale outbreak of clinical cholera occurred in the port city of Madras and surrounding towns in southern India. The etiologic agent proved to be a novel strain of *V. cholerae* belonging neither to the O1 serogroup that typically causes epidemic cholera nor to any of the 137 other serogroups known at the time. This strain spread rapidly up and down the coast of the Bay of Bengal, reaching Bangladesh in December 1992. There alone, it caused more than 100,000 cases of cholera in the first 3 months of 1993. It subsequently spread across the Indian subcontinent and to neighboring countries, affecting Pakistan, Nepal, western China, Thailand, and Malaysia by the end of 1994 (Fig. 159-2). The organism has since been designated *V. cholerae* O139 Bengal in recognition of its novel O antigen and its geographic origin.

The clinical manifestations and epidemiologic features of the disease caused by *V. cholerae* O139 Bengal are indistinguishable from those of O1 cholera. Immunity to the latter, however, is not protective against the former. Thus, although O139 Bengal cholera has been restricted almost exclusively to O1-endemic areas, it has affected patients of all ages, with most cases in adults. Moreover, populations into which *V. cholerae* O139 Bengal has been introduced have responded as virgin populations with respect to severe, lethal cholera. Because naturally acquired immunity to *V. cholerae* O1 does not cross-protect against *V. cholerae* O139 Bengal, vaccines being developed against the former are unlikely to be effective against the latter.

Like the O1 epidemics in cholera-naive areas before it, the O139 epidemic was initially devastating. Some authorities believed that the emergence of *V. cholerae* O139 signaled the beginning of the eighth global cholera pandemic. Indeed, just as O1 El Tor replaced the classical biotype that preceded it, O139 Bengal in 1993 rapidly replaced O1 El Tor as the most common environmental isolate and the predominant cause of clinical cholera in the areas in which it had appeared (Fig. 159-3). However, by the beginning of 1994, O1 El Tor had unexpectedly resumed its dominance in Bangladesh, relegating O139 Bengal cholera to the status of a background endemic infection. In some locales O1 *V. cholerae* remains dominant; in others O139 periodically reemerges. Nevertheless, the potential for global spread of O139 Bengal was underscored by an intercontinental food-borne outbreak that occurred in early 1994 among American and British passengers on a cruise ship in Southeast Asia. Six of the 630 travelers became ill, their symptoms beginning only after they returned home.

## PATHOGENESIS

In the final analysis, cholera is a toxin-mediated disease. Its characteristic watery diarrhea is due to the action of cholera toxin (CTX), a potent protein enterotoxin elaborated by the organism following its colonization of the small intestine. The bacterial properties that facilitate intestinal colonization are incompletely understood. For *V. cholerae* to colonize the small intestine and produce CTX, it must first recognize, contend with, and traverse several hostile environments. The first of these is the acidic milieu of the stomach. To elude the bactericidal effects of gastric acidity, *V. cholerae* relies, at least in part, on a relatively large inoculum size (compared to that needed for colonization by *Shigella*, for instance). The organism must next traverse the mucous layer lining the small bowel. *V. cholerae* chemotaxis and motility and a variety of proteases may allow the organism to traverse this gel covering the intestinal epithelium. Adherence to the intestinal epithelium is believed to be mediated by the toxin-coregulated pilus (TCP), so named because its synthesis is regulated in parallel with that of CTX. Studies of volunteers have established that TCP is essential for *V. cholerae* intestinal colonization. Other *V. cholerae* gene products known to be important in intestinal colonization of experimental animals include accessory colonization factors ABCD, a cell-associated hemagglutinin, iron and magnesium transport proteins, and purine and biotin biosynthesis enzymes.

CTX,TCP, and several other virulence factors, including accessory colonization factors and various outer-membrane proteins, are coordinately regulated by the *toxR* gene product. ToxR protein is a "master switch" that modulates the expression of virulence genes in response to signals that it senses within the environment of the host via a cascade of regulatory proteins. Coordinate regulation of virulence factor expression presumably enables the organism to tailor its repertoire of proteins to suit its needs as it passes from one microenvironment to another. Coordinate regulation of virulence gene expression by a central sensor-effect protein like ToxR has become a paradigm for similar systems that have been discovered in a wide range of pathogenic bacteria.

Once established in the human small bowel, the organism producesCTX, which consists of a monomeric enzymatic moiety (the A subunit) and a pentameric binding moiety (the B subunit). The B pentamer binds to $G_{M1}$ganglioside, a glycolipid on the surface of jejunal epithelial cells that serves as the toxin receptor and makes possible the delivery of the A subunit to its cytosolic target. The activated A subunit ($A_1$) irreversibly transfers ADP-ribose from nicotinamide adenine dinucleotide to its specific target protein, the GTP-binding regulatory component of adenylate cyclase in intestinal epithelial cells. In this configuration, this G protein permanently upregulates the cyclase catalytic subunit; the result is the intracellular accumulation of high levels of cyclic AMP. In intestinal epithelial cells, cyclic AMP inhibits the absorptive sodium transport system in villus cells and activates the excretory chloride transport system in crypt cells, and these events lead to the accumulation of sodium chloride in the intestinal lumen. Since water moves passively to maintain osmolality, isotonic fluid accumulates in the lumen. When the volume of that fluid exceeds the capacity of the rest of the gut to resorb it, watery diarrhea results. Unless the wasted fluid and electrolytes are adequately replaced, shock (due to profound dehydration) and acidosis (due to loss of bicarbonate) follow.

Although perturbation of the adenylate cyclase pathway is the primary mechanism by

whichCTXcauses excess fluid secretion, it is not the only one. Increasing evidence indicates that CTX also enhances intestinal secretion via prostaglandins and/or neural histamine receptors. It is possible that the redundancy of secretory mechanisms activated by CTX accounts for the profound diarrhea and dehydration characteristic of severe cholera.

The genes encodingCTX(*ctxAB*) are part of the genome of a bacteriophage designated CTXF. The receptor for this phage on the *V. cholerae* surface is the essential *V. cholerae* intestinal colonization factorTCP. Following infection of TCP+ *ctxAB*- *V. cholerae* cells, the CTXF genome stably integrates at a specific site on the *V. cholerae* chromosome. Since *ctxAB* is part of a mobile genetic element (CTXF), horizontal transfer of this bacteriophage may account for the emergence of new toxigenic *V. cholerae* serogroups. In addition, since the CTXF receptor TCP is a *V. cholerae* host colonization factor, it is possible that CTXFinfection of TCP+ *ctxAB*- *V. cholerae* strains occurs primarily within the human intestine. Many of the other genes important for *V. cholerae* pathogenicity, including the genes encoding the biosynthesis of TCP, those encoding accessory colonization factors, and those regulating virulence gene expression, are clustered together on one of the two *V. cholerae* chromosomes. This cluster of virulence genes is referred to as the *V. cholerae pathogenicity island*. Similar clustering of virulence genes is found in other bacterial pathogens. It is believed that these pathogenicity islands have been acquired by horizontal gene transfer.

Molecular analysis of *V. cholerae* O139 Bengal has suggested the basis of its origin and the reasons it was able to cause an explosive epidemic of cholera. Both phenotypically and genotypically, O139 Bengal is closely related to the O1 El Tor strains of the seventh pandemic, and it seems to have arisen from them by horizontal gene transfer. It shares the virulence attributes and general pathogenic mechanisms of O1 vibrios, including possession of the sameCTXprophage and the sameTCP. *V. cholerae* O139 Bengal is in fact virtually identical to the seventh-pandemic strains of *V. cholerae* O1 El Tor except for two important differences: production of the novel O139LPS and of an immunologically related O-antigen polysaccharide capsule. Both of these molecules are putative virulence factors, independently enhancing colonization in a murine infection model. The ability to produce the O139 LPS is due to a replacement of a 22-kb DNA segment encoding O1 antigen biosynthesis with a 35-kb segment containing the genes encoding O139 LPS and capsule biosynthesis. Encapsulation is not a feature of O1 strains and may explain the resistance of O139 strains to human serum in vitro as well as the occasional development of O139 bacteremia.

## CLINICAL MANIFESTATIONS

After a 24- to 48-h incubation period, cholera begins with the sudden onset of painless watery diarrhea that may quickly become voluminous and is often followed shortly by vomiting. In severe cases, stool volume can exceed 250 mL/kg in the first 24 h. If fluids and electrolytes are not replaced, hypovolemic shock and death ensue. Fever is usually absent. Muscle cramps due to electrolyte disturbances are common. The stool has a characteristic appearance: a nonbilious, gray, slightly cloudy fluid with flecks of mucus, no blood, and a somewhat sweet, inoffensive odor. It has been called "rice-water" stool because of its resemblance to the water in which rice has been washed. Clinical symptoms parallel volume contraction: At losses of 3 to 5% of normal body weight, thirst

develops; at 5 to 8%, postural hypotension, weakness, tachycardia, and decreased skin turgor are documented; and at >10%, oliguria, weak or absent pulses, sunken eyes (and, in infants, sunken fontanelles), wrinkled ("washerwoman") skin, somnolence, and coma are characteristic. Complications derive exclusively from the effects of volume and electrolyte depletion and include renal failure due to acute tubular necrosis. Thus, if the patient is adequately treated with fluid and salt, complications are averted and the process is self-limited, resolving in a few days.

Laboratory data usually reveal an elevated hematocrit (due to hemoconcentration) in nonanemic patients; mild neutrophilic leukocytosis; elevated levels of blood urea nitrogen and creatinine consistent with prerenal azotemia; normal sodium, potassium, and chloride levels; a markedly reduced bicarbonate level (<15 mmol/L); and an elevated anion gap (due to increases in serum lactate, protein, and phosphate). Arterial pH is usually low (about 7.2).

## DIAGNOSIS

The clinical suspicion of cholera can be confirmed by the identification of *V. cholerae* in stool; however, the organism must be specifically sought. In experienced hands, it can be detected directly by dark-field microscopy on a wet mount of fresh stool, and its serotype can be discerned by immobilization with Inaba- or Ogawa-specific antiserum. Laboratory isolation of the organism requires the use of a selective medium. The best of these is thiosulfate-citrate-bile salts-sucrose (TCBS) agar, on which the organism grows as a flat yellow colony. If a delay in sample processing is expected, Carey-Blair transport medium and/or alkaline-peptone water-enrichment medium should be inoculated as well. In endemic areas there is little need for biochemical confirmation and characterization, although these tasks may be worthwhile in places where *V. cholerae* is an uncommon isolate. Standard microbiologic biochemical testing for Enterobacteriaceae will suffice for identification of *V. cholerae*. All vibrios are oxidase-positive. *V. cholerae* can be distinguished from the otherwise similar *V. mimicus* by its ability to ferment sucrose.

The yield of stool cultures for the diagnosis of *V. cholerae* infection declines late in the course of the illness or when effective antibacterial therapy is initiated. Although not generally evaluable in clinical laboratories, serum vibriocidal antibody titers can be used to confirm the diagnosis in non-cholera-endemic regions of the world. Monoclonal antibody-based diagnostic kits and methods based on the polymerase chain reaction and on DNA probes have been developed for *V. cholerae* O1 and O139 but are unlikely to become available in U.S. clinical laboratories.

## TREATMENT

Cholera is simple to treat; only the rapid and adequate replacement of fluids, electrolytes, and base is required. The mortality rate for appropriately treated disease is usually <1%. However, analysis of a large outbreak of cholera among airline travelers from an endemic country to the United States revealed frequent misdiagnoses by U.S. health professionals and poor appreciation on their part of the principles of management. Compounding these problems was the general unavailability of appropriate oral fluids. Even intravenous fluid therapy typically was not optimal.

It has been proved conclusively that fluid may be given orally. This approach takes advantage of the hexose-$Na^+$cotransport mechanism to move $Na^+$across the gut mucosa together with an actively transported molecule such as glucose. Since $Na^+$losses in the stool are high, a fluid containing $Na^+$ at 90 mmol/L has been recommended by the World Health Organization (WHO) (Table 159-1). This amount of $Na^+$ is higher than that needed to treat diarrhea due to most other causes. The solution is safe, even for infants, if its intake is alternated with the consumption of sodium-free fluids such as breast milk or water. For the sake of simplicity, WHO advises routine use of this single solution for diarrheal disease rather than attempts to choose among multiple formulations according to etiology.

Cereal-based formulations are receiving increased attention as alternative oral rehydration solutions. Because of their lower osmolarity, they may reduce stool output. A mixture with a lower sugar and salt content has also been evaluated in cholera patients, with favorable results. However, concerns have been raised over the safety of its use -- in particular, whether it could cause significant hyponatremia in patients with moderate or severe diarrhea. Because commercial oral rehydration solutions also contain concentrations of glucose and sodium lower than those of theWHOformulation, they should not yet be used routinely to treat cholera.

For initial management of severely dehydrated patients, intravenous fluid replacement is preferable, if available. Because profound acidosis (pH < 7.2) is common in this group, Ringer's lactate is the best choice among commercial products (Table 159-2). It must be used with additional potassium supplements, preferably given by mouth. The total fluid deficit in severely dehydrated patients (³10% of body weight) can be replaced safely within the first 4 h of therapy, half within the first hour. Thereafter, oral therapy can usually be initiated, with the goal of maintaining fluid intake equal to fluid output. However, patients with continued large-volume diarrhea may require prolonged intravenous treatment to keep up with gastrointestinal fluid losses. Severe hypokalemia can develop but will respond to potassium given either intravenously or orally. In the absence of adequate staff to monitor the patient's progress, the oral route of rehydration and potassium replacement is safer than the intravenous route and is physiologically regulated by thirst and urine output.

Although not necessary for cure, the use of an antibiotic to which the organism is susceptible will diminish the duration and volume of fluid loss and will hasten clearance of the organism from the stool. Single-dose tetracycline (2 g) or doxycycline (300 mg) is effective in adults but is not recommended for children under 8 years of age because of possible deposition in bone and developing teeth. Emerging drug resistance is an ever-present concern. For adults with cholera in areas where tetracycline resistance is prevalent, ciprofloxacin -- either in a single dose (30 mg/kg, not to exceed a total dose of 1 g) or in a short course (15 mg/kg bid for 3 days, not to exceed a total daily dose of 1 g) -- or erythromycin (a total of 40 mg/kg daily in three divided doses for 3 days) is a clinically effective substitute. Both drugs are highly effective in reducing total stool output, and each is significantly better than trimethoprim-sulfamethoxazole. Because of the high cost of quinolones,WHOrecommends erythromycin as the first alternative to tetracycline. For children, furazolidone has been the recommended agent and trimethoprim-sulfamethoxazole the second choice. It is of note that *V. cholerae* O139 is

often resistant to both of these drugs but is susceptible to quinolones, erythromycin, tetracycline, and ampicillin (among others). Because of cost and/or toxicity issues related to the other drugs, erythromycin is a good choice for pediatric cholera, especially where O139 Bengal is present. The efficacy of single-dose erythromycin therapy for cholera has not been demonstrated.

## CONTROL

In outbreaks, efforts should first be made to identify case contacts and to treat incubating carriers. Next, epidemiologic studies should be undertaken to establish the modes of transmission to define the best strategy to interrupt them. Both the establishment of rehydration centers and instruction in rehydration techniques are essential to the reduction of mortality. Immunization in these circumstances is not an effective means of control.

## PREVENTION

Provision of safe water and facilities for sanitary disposal of feces, improved nutrition, and attention to food preparation and storage in the household could significantly reduce the incidence of cholera. Much effort has been devoted to the development of an effective cholera vaccine over the past two decades, with a particular focus on oral vaccine strains. Traditional killed cholera vaccine given intramuscularly provides little protection to nonimmune subjects and predictably causes adverse effects, including pain at the injection site, malaise, and fever. The vaccine's limited efficacy is at least partially due to its failure to induce a local immune response at the intestinal mucosal surface.

Two types of oral cholera vaccines are under development. The first is a killed whole-cell (WC) vaccine. Two formulations of the killed WC vaccine have been prepared: one that also contains the nontoxic B subunit of CTX (WC/BS) and one composed solely of killed bacteria. In field trials in Bangladesh, both of the killed vaccines were compared with placebo and conferred ~50% protection over a 3-year evaluation period. The protective efficacy of WC/BS was superior to that of WC during the initial 8 months of follow-up (69 versus 41%) but equivalent or inferior thereafter. Immunity was relatively sustained in persons vaccinated at an age of>5 years but was not well sustained in younger vaccinees.

The second approach is that of a live attenuated vaccine strain developed, for example, by the isolation or creation of mutants lacking activeCTX. Three criteria must be met in live vaccine design: The vaccine strain must induce protective immunity, it must be safe to administer, and it must be minimally reactogenic. *Safety criteria* include the vaccine strain's potential to regain virulence, either spontaneously or via horizontal gene transfer from environmental strains, as well as its potential to donate virulence genes to other strains. *Reactogenicity* refers to its potential to cause symptoms such as fever or diarrhea in vaccinees.

Strain CVD 103-HgR, an oral live cholera vaccine licensed for immunization of travelers in Europe, is derived from a classical biotype strain of *V. cholerae* by the deletion of theCTX A subunit gene and the insertion in the hemolysin gene of a mercury resistance

marker. This strain has been extensively tested in volunteers; although it is poorly excreted in the stool of human vaccinees, a single dose produces a significant increase in the titer of vibriocidal antibody in ~75% of recipients, including children between the ages of 2 and 4 years, with almost no reactogenicity. Studies in volunteers demonstrate that this vaccine is more effective against classical than against El Tor cholera. Unfortunately, in a large field trial in Indonesian children, this vaccine failed to induce protection against clinical cholera.

Other live attenuated vaccine candidate strains have been prepared from El Tor and O139 *V. cholerae*. In studies in volunteers, these vaccine strains have often exhibited significant reactogenicity whose cause (given the absence of activeCTX) is unclear. Reactogenicity may result from the production of another toxic moiety (e.g., the hemagglutinin/protease or the RTX toxin) by the live attenuated strain. Alternatively, intestinal colonization itself may result in reactogenicity. These El Tor- and O139-derived live vaccine strains are therefore at least several years away from potential licensing. Because of the minimal efficacy of existing parenteral vaccines, cholera immunization is recommended for U.S. travelers only if it is mandated by the countries they plan to visit.

## OTHER *VIBRIO* SPECIES

In recent years, the taxonomic, epidemiologic, pathophysiologic, and clinical features of vibrios that do not cause clinical cholera have become increasingly well understood. Ten human pathogens are currently recognized in the genus *Vibrio*. Included are species associated primarily with gastrointestinal illness (*V. parahaemolyticus*, non-O1 *V. cholerae*, *V. mimicus*, *V. fluvialis*, *V. hollisae*, and *V. furnissii*) and species associated primarily with soft tissue infections (*V. vulnificus*, *V. alginolyticus*, and *V. damsela*). In addition, *V. vulnificus* has emerged as a cause of primary sepsis in certain compromised hosts. Vibrios are abundant in coastal waters the world over and tend to concentrate in the tissues of filter-feeding mollusks. Under optimal conditions, some can double in number in as little as 9 min. Consequently, seawater and raw or undercooked shellfish are important sources of human infection (Table 159-3). Vibrios grow best at temperatures of 28°C to 44°C but not at all below 4°C or above 60°C. Most can be cultured on blood or MacConkey agar, each of which contains enough salt to support the growth of the halophilic organisms (³0.5%). As with *V. cholerae*,TCBS is the best selective medium. The species can be differentiated in the laboratory by standard biochemical tests. The most important members of the group are *V. parahaemolyticus* and *V. vulnificus*. These and selected other species are considered below in greater detail.

### SPECIES ASSOCIATED PRIMARILY WITH GASTROINTESTINAL ILLNESS

***V. parahaemolyticus*** First implicated as a cause of enteritis by Japanese workers in 1953, *V. parahaemolyticus* is now recognized as an important intestinal pathogen in many parts of the world. In one study from Japan, 24% of reported cases of food poisoning were attributed to this organism, presumably owing to the widespread consumption of raw seafood there. In the United States, *V. parahaemolyticus* has been responsible for several well-documented common-source outbreaks of diarrhea, typically linked to ingestion of undercooked or improperly handled seafood or of other

foods that have been contaminated by seawater. Most reports have come from the Atlantic Coast, the Gulf of Mexico, and Hawaii. The organism is ubiquitous in marine environments and is able to grow in saline concentrations as high as 8 to 10%. The ability to cause hemolysis on Wagatsuma agar (known as the *Kanagawa phenomenon*) is closely linked to enteropathogenicity. In one study, 96.5% of isolates from patients with diarrhea were hemolytic versus only ~1% of isolates from seawater. Hemolysis is attributed to a 42-kDa heat-stable protein, the exact pathophysiologic role of which is uncertain. The mechanism by which *V. parahaemolyticus* causes diarrhea is not clear.

*V. parahaemolyticus* has been associated with two distinct gastrointestinal presentations. The more common is a syndrome of watery diarrhea, accompanied in most cases by abdominal cramps, nausea, and vomiting and in about one-quarter of cases by fever and chills. The incubation period ranges from 4 h to 4 days, and the symptomatic period lasts for a median of 3 days. The vast majority of North American cases have been of this type. The less common syndrome is one of dysentery, described in India and Bangladesh and characterized by severe abdominal cramps, nausea, vomiting, and bloody or mucoid stools. Most cases of either type are self-limited and require neither antimicrobial treatment nor hospitalization. Severe infections are associated with underlying diseases, including diabetes, preexisting liver disease, iron-overload states, or immunosuppression. The occasional severe case should be treated with fluid replacement and antibiotics, as described above for cholera. Death is very rare. There are no reliable differential diagnostic features. *V. parahaemolyticus* should be considered as a possible cause in all cases of diarrhea that can be epidemiologically linked to seafood consumption or to the sea itself.

In addition to gastrointestinal disease, *V. parahaemolyticus* is a rare cause of extraintestinal infections, including wound infections, otitis, and -- very rarely -- sepsis.

**Non-O1 *V. cholerae*** The heterogeneous non-O1 *V. cholerae* organisms are biochemically indistinguishable from *V. cholerae* O1 on routine testing but fail to agglutinate in O1 antiserum. While technically a non-O1 vibrio, *V. cholerae* O139 Bengal is not grouped with these pathogens because of its potential to cause epidemic cholera, as detailed above. Non-O1 *V. cholerae* strains have been responsible for several well-described food-borne outbreaks of gastroenteritis as well as for sporadic cases of otitis media, wound infection, and bacteremia. About half of all U.S. isolates are obtained from stool specimens. Like other vibrios, non-O1 *V. cholerae* organisms are widely distributed in marine environments; unlike most other vibrios, however, they require only trace amounts of NaCl to survive (i.e., they are nonhalophilic). Recognized U.S. cases invariably have been associated either with the consumption of raw oysters or with recent travel, typically to Mexico. The clinical spectrum of diarrheal disease caused by non-O1 *V. cholerae* is broad and likely reflects the heterogeneous virulence attributes of the group. Occasional isolates make a protein enterotoxin very similar toCTX. Others produce cytotoxins, hemolysins, or invasins.

Gastroenteritis due to non-O1 *V. cholerae* typically has an incubation period of<2 days. Stools may be copious and watery. On occasion, diarrhea may leave the patient severely dehydrated, as in cholera. Alternatively, the stools may be partly formed, less voluminous, and bloody or mucoid. Abdominal cramps, nausea, vomiting, and fever are often reported. In one series, 11% of patients were hospitalized; in another, the figure

was 50%. The duration of illness ranges from about 2 to 7 days. As in cholera, patients with significant dehydration should be treated with oral or intravenous fluids. The role of antibiotics is uncertain.

Wound infection and otitis media each account for ~10% of non-O1 *V. cholerae* isolates. Bacteremia accounts for another 20%. Patients with extraintestinal infection often have a history of occupational or recreational exposure to seawater. Bacteremia is more likely to develop in the presence of liver disease. Extraintestinal infections should be treated with antibiotics. There is a paucity of information to guide the choice of a specific agent and schedule. Most strains are sensitive in vitro to tetracycline, chloramphenicol, and other agents.

## SPECIES ASSOCIATED PRIMARILY WITH SOFT TISSUE INFECTION OR BACTEREMIA

***V. vulnificus*** Though it represents only a small minority of the *Vibrio* species found in nature (4% of Atlantic Coast isolates in one study), *V. vulnificus* is perhaps the most important cause of severe *Vibrio* infections in the United States (0.8 cases per 100,000 population in one study from Louisiana). Formerly included in the species *V. parahaemolyticus*, *V. vulnificus* was distinguished in the 1970s by its ability to ferment lactose and to cause distinct clinical syndromes. Like most vibrios, it proliferates in the warm summer months. It requires a saline environment for growth but prefers concentrations lower than those preferred by *V. parahaemolyticus* and *V. alginolyticus* (range, up to ~8%; optimal, ~1%). Infections in humans typically occur in coastal states between May and October and most often involve men over age 40. *V. vulnificus* has been linked unequivocally to two distinct syndromes: primary sepsis, typically in patients with antecedent liver disease, and primary wound infections, usually in people without underlying disease. Some authors have suggested that this organism causes gastroenteritis, but the evidence for this association is tenuous.

*V. vulnificus* is remarkably invasive in animal models. It is endowed with a number of virulence attributes, including an antiphagocytic capsule, serum resistance, a cytotoxin/hemolysin (the organism is Kanagawa-positive), collagenase, elastolytic protease, phospholipase, and siderophores. Its virulence, as measured by the 50% lethal dose in mice, is markedly enhanced under conditions of iron overload, a fact consonant with its propensity to infect patients with hemochromatosis.

Primary sepsis occurs most commonly in patients with cirrhosis or hemochromatosis but has also developed in patients with hematopoietic disorders or chronic renal insufficiency, in persons using immunosuppressive medications or alcohol, and (rarely) in individuals without apparent underlying disease. Most of those affected have ingested raw oysters within 2 days of onset (median incubation period, 16 h). The process begins precipitously with malaise, chills, fever (mean temperature, 39.8°C), and prostration. Hypotension develops in one-third of cases, often by the time of admission. Cutaneous manifestations, which develop in three-quarters of cases (usually by 36 h after onset), typically involve the extremities -- lower more often than upper (Fig. 159-CD1). A common sequence is the evolution of erythematous patches followed by ecchymoses, vesicles, and bullae. (Indeed, the presence of sepsis and bullous skin lesions suggests the diagnosis in an appropriate setting.) Necrosis and sloughing may occur. Laboratory

study reveals leukopenia more often than leukocytosis, thrombocytopenia, and (occasionally) elevated levels of fibrin split products. *V. vulnificus* can be cultured from blood or cutaneous lesions.

Mortality approaches 50%, with most deaths due to uncontrolled sepsis. Accordingly, prompt treatment is critical and should include empirical antibiotic administration, aggressive debridement, and general supportive care. *V. vulnificus* is sensitive to a number of antimicrobials in vitro, including tetracycline, gentamicin, and third-generation cephalosporins. No compelling clinical data from studies of humans support the preferential use of any one of these agents. Tetracycline is demonstrably superior in a murine model and on that basis is considered the drug of choice (0.5 to 1 g intravenously every 12 h), either alone or in combination with gentamicin. The duration of therapy is guided by the clinical response.

Wound infections with *V. vulnificus* can develop in patients with or without underlying disease and invariably follow contact of seawater with either a prior or a fresh wound. The incubation period is brief (4 h to 4 days; mean, 12 h). The disease begins with swelling, erythema, and -- in many cases -- intense pain around the wound. Rapidly spreading cellulitis follows, with vesicular, bullous, or necrotic lesions developing in some instances. Metastatic events do not generally occur. Fever (median temperature, 38.9°C) and leukocytosis are demonstrable in most cases. The organism can be cultured from skin lesions and occasionally from blood. Prompt antibiotic therapy and debridement are usually curative.

***V. alginolyticus*** This species was first recognized as a human pathogen in 1973 and is now known to cause occasional wound, ear, and eye infections. It is the most salt-tolerant of the vibrios, able to grow in concentrations >10%. Most clinical isolates come from superinfected wounds, which presumably became contaminated at the beach. Infection varies in severity but is generally not serious and responds well to antibiotic therapy and drainage. A few reports have described otitis externa, otitis media, or conjunctivitis. Therapy with tetracycline is usually curative. *V. alginolyticus* is a rare cause of bacteremia in immunocompromised hosts.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 160. BRUCELLOSIS - *M. Monir Madkour*, *Dennis L. Kasper*

### DEFINITION

Brucellosis is a zoonosis transmitted to humans from infected animals. Its clinical features are not disease specific. *Brucellosis* has many synonyms derived from the geographical regions in which the disease occurs (e.g., Mediterranean fever, Malta fever, Gibraltar fever, Cyprus fever); from the remittent character of its fever (e.g., undulant fever); or from its resemblance to malaria and typhoid (e.g., typhomalarial fever, intermittent typhoid).

### ETIOLOGY

Human brucellosis can be caused by any of four species: *Brucella melitensis* (the most common and most virulent cause of brucellosis worldwide) is acquired primarily from goats, sheep, and camels; *B. abortus* from cattle; *B. suis* from hogs; and *B. canis* from dogs. These small aerobic gram-negative bacilli are unencapsulated, nonmotile, non-spore-forming, facultative intracellular parasites that cause lifelong infection in animals. Brucellae are killed by boiling or pasteurization of milk and milk products. They survive for up to 8 weeks in unpasteurized, white, soft cheese made from goat's milk and are not killed by freezing. The organisms remain viable for up to 40 days in dried soil contaminated with infected-animal urine, stool, vaginal discharge, and products of conception and for longer periods in damp soil.

### EPIDEMIOLOGY

The global incidence of human brucellosis is not known because of the variable quality of disease reporting and notification systems in many countries. Worldwide, the only countries believed to be free of brucellosis are Norway, Sweden, Finland, Denmark, Iceland, Switzerland, the Czech and Slovak republics, Romania, the United Kingdom (including the Channel Islands), the Netherlands, Japan, Luxembourg, Cyprus, and Bulgaria; the U.S. Virgin Islands are also free of the disease. Reports indicate that, even in developed nations, the true incidence of brucellosis may be up to 26 times higher than official figures suggest. In the United States, about 200 new cases are reported every year; however, it is estimated that only 4 to 10% of cases are recognized and reported. Consumption of imported cheese, travel abroad, and occupation-related exposures are the most frequently identified sources of infection. In communities where brucellosis is endemic, the disease occurs in children and the family members of infected persons are at risk. Even in countries where animal brucellosis is controlled, the disease occasionally develops among farmers, meat-processing workers, veterinarians, and laboratory workers.

The *Brucella* organism is transmitted most commonly through the ingestion of untreated milk or milk products; raw meat (i.e., blood) and bone marrow have also been implicated. However, the organism can be contracted via inhalation during contact with animals, especially by children and by slaughterhouse, farm, and laboratory workers. Other routes of infection for at-risk workers include skin abrasion, autoinoculation, and conjunctival splashing. The organism has occasionally been transmitted from person to person through the placenta, during breast-feeding, and during sexual activity.

Aerosolized *B. melitensis* is a classic agent of biological warfare.

## PATHOGENESIS AND IMMUNITY

Serum opsonizes *Brucella* organisms for ingestion by polymorphonuclear leukocytes and activated macrophages. Brucellae resist intracellular phagocytic killing by mechanisms such as the suppression of the myeloperoxide-hydrogen peroxide-halide system and the production of superoxide dismutase. The pathogen-phagocyte interaction plays a key role in determining the severity and outcome of brucellosis. The organisms surviving within and escaping from the phagocytes multiply and reach the bloodstream via the lymphatics, subsequently localizing in the liver, spleen, bones, kidneys, lymph nodes, heart valves, nervous system, and testes. In these organs, the bacteria are ingested by macrophages and survive by inhibition of phagosome-lysosome fusion. In infected tissues, inflammatory responses or noncaseating granulomas typically develop, and caseating granulomas and abscesses have been described.

Cytokines, including interleukin (IL) 1, IL-12, and tumor necrosis factor, appear to be important in host defense against *Brucella* infection. The smooth lipopolysaccharide (LPS) of *Brucella* is the major known virulence factor. Strains with rough LPS are more likely than those with smooth LPS to be lysed by nonimmune serum. In virulent strains, the foremost target for specific antibodies is the LPS. Serum IgM antibodies to LPS appear within 1 week after infection and are followed later by IgG and IgA. Titers of both IgM and IgG antibody fall after treatment, and failure of these titers to decline should prompt an evaluation for relapse or persistent infection.

## CLASSIFICATION

Brucellosis is classified according to whether or not the disease is active (i.e., symptoms or progressive tissue damage and significantly raised *Brucella* agglutinin levels with or without positive cultures) and whether or not there is localized infection. The state of activity and the site of localization have a significant impact on recommended treatment. Classification of brucellosis as acute, subacute, serologic, bacteremic, or of mixed types serves no purpose in diagnosis and management.

## CLINICAL MANIFESTATIONS AND COMPLICATIONS

Brucellosis is a systemic disease with protean manifestations. Its features may mimic those of other febrile illnesses. The incubation period lasts for about 1 to 3 weeks but may be as long as several months, depending on the virulence of the organisms, their route of entry, the infecting dose, and the host's preexisting health status. The onset of symptoms may be either abrupt (over 1 to 2 days) or gradual (³1 week). The most common symptoms are fever, chills, diaphoresis, headaches, myalgia, fatigue, anorexia, joint and low-back pain, weight loss, constipation, sore throat, and dry cough. Physical examination often reveals no abnormalities, and patients can look deceptively well. Some patients, in contrast, are acutely ill, with pallor, lymphadenopathy, hepatosplenomegaly, arthritis, spinal tenderness, epididymoorchitis, rash, meningitis, cardiac murmurs, or pneumonia. The fever of brucellosis has no distinctive pattern but may exhibit diurnal variation, with normal temperatures in the morning and high

temperatures in the afternoon and evening. Localization to an organ or a system may be evident at the onset of the disease.Table 160-1 lists the frequencies of key historic features, symptoms, and signs among 500 patients with brucellosis due to *B. melitensis*.

**Bones and Joints** Although monarticular septic arthritis occurs, 30 to 40% of patients have reactive asymmetric polyarthritis involving the knees, hips, shoulders, and sacroiliac and sternoclavicular joints. The total white cell count in synovial fluid ranges from 4000 to 40,000/mL, typically with about 60% polymorphonuclear leukocytes. The synovial fluid glucose concentration may be reduced and the protein concentration elevated; cultures of synovial fluid are positive in about 50% of cases.

Infection with *Brucella* organisms commonly causes osteomyelitis of the lumbar vertebrae, starting at the superior end plate (an area with a rich blood supply) and occasionally progressing to involve the entire vertebra, disk space, and adjacent vertebrae. Extraspinal *Brucella* osteomyelitis is rare. In *Brucella* septic arthritis and osteomyelitis, the peripheral white cell count is typically normal, while the erythrocyte sedimentation rate may be either normal or elevated.

**Heart** Cardiovascular complications of brucellosis include endocarditis, myocarditis, pericarditis, aortic root abscess, mycotic aneurysms, thrombophlebitis with pulmonary aneurysm, and pulmonary embolism. *Brucella* endocarditis may develop on valves previously damaged by rheumatic fever or congenital malformation but also occurs on previously normal valves. The clinical features are indistinguishable from those of endocarditis caused by other organisms (Chap. 126). Endocarditis is the leading cause of death in brucellosis, although the outcome of *Brucella* endocarditis has been more favorable in recent years because of advances in early diagnosis, antibiotic treatment, and cardiac surgery. Physicians who suspect brucellae as a cause of culture-negative endocarditis in patients with possible environmental exposure should notify the bacteriology laboratory performing the blood culture so that extended incubation, specific media, and biohazard precautions can be employed.

**Respiratory Tract** Brucellae can produce respiratory symptoms. A flulike illness with sore throat, tonsillitis, and dry cough is common and usually mild. Hilar and paratracheal lymphadenopathy, pneumonia, solitary or multiple pulmonary nodules, lung abscess, and empyema have been reported.

**Gastrointestinal Tract and Hepatobiliary System** Gastrointestinal manifestations of *Brucella* infection are generally mild and may include nausea, vomiting, constipation, acute abdominal pain, and/or diarrhea. Pathologic examination of the liver may reveal any of several changes, including noncaseating granulomas (Fig. 160-CD1), suppurative abscesses, mononuclear cell infiltration, or hyperemia of the intestinal mucosa. Acute ileitis with inflammation of Peyer's patches and colitis have been reported. Hepatic and splenic enlargement may be documented in 15 to 20% of cases, and abscesses may develop in the liver and spleen. Infected ascites, pancreatitis, and cholecystitis have been reported. Mild jaundice may be evident, with elevated levels of bilirubin and hepatic enzymes.

**Genitourinary Tract** The various genitourinary infections attributed to brucellae include unilateral or bilateral epididymoorchitis, which is rarely associated with testicular

abscess. Prostatitis, seminal vesiculitis, dysmenorrhea, amenorrhea, tuboovarian abscess, salpingitis, cervicitis, acute pyelonephritis, glomerulonephritis, and massive proteinuria have also been documented. *Brucella* organisms have been cultured from the urine in up to 50% of cases of genitourinary tract infection.

**Central Nervous System** Neurobrucellosis is uncommon but serious and includes meningitis, meningoencephalitis, multiple cerebral or cerebellar abscesses, ruptured mycotic aneurysms, myelitis, Guillain-Barre syndrome, cranial nerve lesions, hemiplegia, sciatica, myositis, and rhabdomyolysis. Papillitis, papilledema, retrobulbar neuritis, optic atrophy, and ophthalmoplegia due to lesions in cranial nerves III, IV, and VI may occur in *Brucella* meningoencephalitis. Cerebrospinal fluid (CSF) pressure is usually elevated; the fluid may appear clear, turbid, or hemorrhagic; the protein concentration and cell count (predominantly lymphocytes) are elevated; and the glucose concentration may be either reduced or normal. In *Brucella* meningitis, which can occur at any time during the course of the disease, the organism may be cultured from the CSF.

**Other Manifestations** Conjunctival splashing with live attenuated *B. abortus* vaccine (S19) during animal vaccination may cause conjunctivitis, keratitis, and corneal ulcers, with progression to systemic disease in some cases. Uveitis, optic neuritis, retinopathy, retinal detachment, and endophthalmitis may result from hematogenous spread.

Skin manifestations of brucellosis are uncommon. They include maculopapular eruptions, purpura and petechiae, chronic ulcerations, multiple cutaneous and subcutaneous abscesses, discharging sinuses, superficial thrombophlebitis, erythema nodosum, and pemphigus.

Brucellosis during human pregnancy can cause abortion or intrauterine fetal death. Brucellae have been isolated from the human placenta, fetus, and newborn.

The bone marrow of *Brucella*-infected patients frequently contains noncaseating granulomas. Among the hematologic complications of brucellosis are anemia, leukopenia, and thrombocytopenia.

Endocrinologic findings reported in brucellosis include thyroiditis with abscess formation, adrenal insufficiency, and the syndrome of inappropriate secretion of antidiuretic hormone.

## DIAGNOSIS

The combination of potential exposure, consistent clinical features, and significantly raised levels of *Brucella* agglutinin (with or without positive cultures of blood, body fluid, or tissues) confirms the diagnosis of active brucellosis. The organism's identity is confirmed by phage typing, DNA characterization, or metabolic profiling. Use of a $CO_2$detection system (such as BACTEC; Becton Dickinson, Sparks, MD) for blood culture provides a more sensitive and rapid culture result than standard methods, with positivity usually apparent after only 2 to 5 days of incubation. Serum antibodies to *Brucella* can be detected by several methods, including standard tube agglutinins (STA), the 2-mercaptoethanol agglutination test, Coombs' test, enzyme-linked immunosorbent

assay, and polymerase chain reaction (PCR). *B. abortus* antigens, which are commonly used for serologic tests, cross-react with *B. melitensis* and *B. suis* but not with *B. canis*. The specific antigen required for assay of antibodies to *B. canis* is not commercially available. *B. canis* antibody titers can be determined in the United States at the Centers for Disease Control and Prevention in Atlanta. A false-negative result in the STA may be obtained because of the prozone phenomenon, which can be avoided by testing of sera at both low and high dilutions.

In endemic areas a *Brucella* antibody titer of 1:320 or 1:640 is significant, while in nonendemic areas an antibody titer of 1:160 is considered significant. Detection of elevated levels of antibody to *Brucella* organisms in the absence of symptoms during the screening of potential blood donors is common in endemic areas. To establish a diagnosis in these regions, clinical and serologic evaluation should be repeated after 2 to 4 weeks and a further rise in titer sought. A high titer of specific IgM suggests recent exposure, while a high titer of specific IgG suggests active disease. Lower titers of IgG may indicate past exposure or treated infection.

Cooperation and consultation with a clinical microbiology laboratory are important when brucellosis is suspected. It may be necessary to observe culture bottles for up to 6 weeks before organisms become detectable. Subcultures should be prepared on duplicate blood agar plates (with and without an atmosphere of 10% $CO_2$) and special media (such as a blood- or serum-enriched peptone-based medium) or with a rapid $CO_2$detection system. Patients whose blood or bone marrow is cultured are positive at one site or the other in 50 to 70% of cases. The peripheral white cell count is usually normal but may be low, with relative lymphocytosis. Thrombocytopenia and disseminated intravascular coagulation may be documented. Levels of hepatic enzymes and serum bilirubin may be raised.

Radiologic investigations aimed at detecting skeletal involvement include plain radiography, bone scintigraphy, computed tomography (CT), and magnetic resonance imaging (MRI). Bone scintigraphy is more sensitive than conventional radiography in detecting areas of spinal and extraspinal involvement, particularly in the early stage of infection. CT is useful for further evaluation of spinal lesions and of the extension of infection into the spinal canal. MRI is the modality of choice for the assessment of *Brucella* spondylitis and is more sensitive than scintigraphy or CT for demonstration of the extent of disease.

Plain lateral radiography of the spine may reveal bone sclerosis, with destruction and erosion of the superior end plate anteriorly. As the disease progresses, healing with osteophyte formation and reduction of disk space may take place. In *Brucella* septic monarthritis, plain radiography may show effusion and soft tissue swelling without bone or joint destruction. Scintigraphy may document increased uptake in sacroiliac joints or lumbar vertebrae, even when plain radiography gives normal results.MRIshows diffuse high-signal intensity of the affected vertebrae and may reveal narrowing of the spinal canal as well as loss of definition of the posterior aspect of the vertebrae.

## TREATMENT

Single-agent therapy for brucellosis has now been abandoned because of the high rates

of failure and relapse and the potential development of antibiotic resistance. Relatively short courses (<8 weeks) of treatment with antibiotic combinations have similarly been associated with high rates of relapse. The combination of doxycycline and an aminoglycoside (gentamicin, streptomycin, or netilmicin) for 4 weeks followed by the combination of doxycycline and rifampin for 4 to 8 weeks is the most effective regimen. Doxycycline (which is preferred over tetracycline) is given orally in a dose of 100 mg twice daily. Gentamicin is given intramuscularly or as a slow intravenous infusion (3 to 5 mg/kg per day in divided doses every 8 h). Netilmicin (which is preferred to streptomycin) is given (intramuscularly to outpatients, intravenously to inpatients) in a dose of 2 mg/kg every 12 h; trough levels in plasma should be monitored regularly and maintained at£2 ug/mL. Streptomycin is given intramuscularly in a dose of 1 g once daily to patients under 45 years of age and in a dose of 0.5 to 0.75 g/d to older patients. Tetracycline is given orally in a dose of 250 mg every 6 h and rifampin as a single daily dose of 600 to 900 mg. An alternative regimen consists of the doxycycline/rifampin combination given for 8 to 12 weeks. The doxycycline/aminoglycoside combination is more effective than the doxycycline/rifampin combination in that rifampin reduces levels of doxycycline in plasma.

Patients with serious complications of brucellosis require urgent surgical and medical treatment. These complications include endocarditis, aortic root abscesses, mycotic aortic aneurysms, meningitis, cerebral or cerebellar abscesses, spinal or extraspinal osteomyelitis, and liver or splenic abscess. These patients should be hospitalized and given first a three-drug regimen -- i.e., oral doxycycline with intravenous aminoglycoside and rifampin -- for 4 weeks and then a two-drug regimen -- i.e., doxycycline and rifampin -- for 8 to 12 weeks. In instances of renal failure, doxycycline (at adjusted doses) can be used safely. In contrast, the use of aminoglycosides requires facilities for the monitoring of plasma levels; if such facilities are not available, then the doxycycline/rifampin combination should be administered for 8 to 12 weeks.

When used alone, fluoroquinolones (which exhibit good intracellular penetration and efficacy against *Brucella* organisms in vitro) have been associated with the development of quinolone resistance and with high rates of failure and relapse. At present, clinical data are inadequate for the formulation of recommendations regarding the combination of fluoroquinolones with doxycycline, rifampin, or streptomycin.

Third-generation cephalosporins (e.g., ceftriaxone), although active in vitro against brucellae when used alone, have also been associated with a high incidence of clinical failure and relapse. These agents may be useful in combination with other drugs for the treatment of *Brucella* meningitis.

In pregnancy, trimethoprim-sulfamethoxazole (TMP-SMZ) can be given in combination with rifampin for 8 to 12 weeks. The TMP-SMZ dosage appropriate for pregnant women is two or three tablets every 12 h (each tablet contains 80 mg of TMP and 400 mg of SMZ). Children below the age of 8 years can also be treated with rifampin and TMP-SMZ for 8 to 12 weeks, while older children should receive the same antibiotics as adults in the following doses: doxycycline, 100 mg/d orally; an aminoglycoside (gentamicin, 2 mg/kg per day in divided doses every 8 h); and rifampin, 15 mg/kg per day orally or by slow intravenous infusion. TMP-SMZ is given orally every 12 h in a dose that depends on the patient's age (birth to 6 months, 120 mg; 6 months to 6 years, 240

mg).

Within 4 to 14 days after the initiation of therapy, patients become afebrile and constitutional symptoms disappear. The enlarged liver and spleen return to their normal size within 2 to 4 weeks. An acute, intense flare-up of symptoms may follow the start of treatment, especially that with tetracyclines. This reaction is transient and does not necessitate the discontinuation of therapy. In endemic areas the coexistence of brucellosis and tuberculous spondylitis may result in a failure to respond to appropriate treatment. Treated patients whose infections are apparently cured should be followed clinically and serologically, with repeat blood cultures, every 3 to 6 months for 2 years.

**PREVENTION**

Efforts at prevention should be aimed at the source of infection. Immunization of animals and boiling or pasteurization of milk and milk products are important. Workers in the meat and dairy industries in the former Soviet Union, China, and France have been vaccinated; the vaccine (two injections given 2 weeks apart, each containing 1 mg of an insoluble fraction of phenol-extracted bacteria) markedly reduces the rate of infection. However, the vaccine induces fever in 6% of recipients and severe pain at the injection site in 16%. Moreover, immunity is short-lived, and vaccination should be repeated every 2 years. This vaccine is not used in the United States.

**PROGNOSIS**

Deaths attributable to brucellosis should be avoidable. Even before the discovery of antibiotics, the mortality rate was <2% and endocarditis was most frequently the cause of death. Morbidity due to brucellosis remains significant; its severity depends on the infecting *Brucella* species and is greatest with *B. melitensis*. Spinal damage, paraplegia, and other neurologic deficits may occur. Nerve deafness due to meningitis or secondary to treatment with streptomycin has been documented.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 161. TULAREMIA - *Richard F. Jacobs*

### DEFINITION

Tularemia is a zoonosis caused by *Francisella tularensis*, so named in 1974 in recognition of the contributions of Edward Francis. Humans of any age, sex, or race are universally susceptible to this systemic infection. Tularemia is primarily a disease of wild animals and persists in contaminated environments, ectoparasites, and animal carriers. Human infection is incidental and usually results from interaction with biting or blood-sucking insects, wild or domestic animals, or the environment. Tularemia is common in Arkansas, Oklahoma, and Missouri, where more than 50% of the cases in the United States occur. An increasing number of cases of tularemia have been reported from the Scandinavian countries, eastern Europe, and Siberia. The illness is characterized by various clinical syndromes, the most common of which consists of an ulcerative lesion at the site of inoculation, with regional lymphadenopathy and lymphadenitis. Systemic manifestations, including pneumonia, typhoidal tularemia, and fever without localizing findings, pose a greater diagnostic challenge.

### ETIOLOGY AND EPIDEMIOLOGY

*F. tularensis* is the etiologic agent of tularemia, which, with rare exceptions, is the only disease produced by this genus. The organism is a small, gram-negative, pleomorphic, nonmotile, non-spore-forming bacillus measuring 0.2 um by 0.2 to 0.7 um. Bipolar staining results in a coccoid appearance. The organism is a thinly encapsulated, nonpiliated strict aerobe that invades host cells.

In nature, *F. tularensis* is a hardy organism that persists for weeks or months in mud, water, and decaying animal carcasses. Dozens of biting and blood-sucking insects, especially ticks and tabanid flies, serve as vectors. Ticks and wild rabbits are the source for most of the human cases in the endemic areas of the southeastern United States and the Rocky Mountain states. In Utah, Nevada, and California, tabanid flies are the most common vectors. Animal reservoirs include wild rabbits, squirrels, birds, sheep, beavers, muskrats, and domestic dogs and cats.

The two main biovars of *F. tularensis* -- *tularensis* (type A) and *palearctica* (type B) -- are both found in the United States. Type A produces more serious disease in humans; without treatment, the associated fatality rate is approximately 5%. Type B produces a milder, often subclinical infection that is usually contracted from water or marine mammals. Although all strains appear serologically identical, individual strains may possess varying degrees of virulence. *F. tularensis* does not produce an exotoxin, but an endotoxin similar to that of other gram-negative bacilli has been identified. The progression of illness depends upon the organism's virulence, the inoculum size, the portal of entry, and the host's immune status.

Ticks pass the organism to their offspring via a transovarian route. The organism is found in tick feces but not in large quantities in tick salivary glands. In the United States, the disease can be carried by *Dermacentor andersoni* (Rocky Mountain wood tick), *D. variabilis* (American dog tick), *D. occidentalis* (Pacific coast dog tick), and *Amblyomma americanum* (Lone Star tick). *F. tularensis* is transmitted frequently during blood meals

taken by embedded ticks following hours of attachment. It is the taking of a blood meal through a fecally contaminated field that transmits the organism. Tularemia is more common among men than among women. Person-to-person transmission is rare or nonexistent. Transmission of the organism by ticks and tabanid flies takes place mainly in the spring and summer. However, continued transmission in the winter months by trapped or hunted animals has been documented. The organism is extremely infectious. Biosafety level 2 is recommended for clinical laboratory work with material whose contamination is suspected, and biosafety level 3 is required for culture of the organism in large quantities.

## PATHOGENESIS AND PATHOLOGY

The most common portal of entry for human infection is through skin or mucous membranes, either directly -- through the bite of ticks, other arthropods, or other animals -- or via inapparent abrasions. Inhalation or ingestion of *F. tularensis* can also result in infection. Although more than $10^8$ organisms are usually required to produce infection via the oral route (oropharyngeal or gastrointestinal tularemia), fewer than 50 organisms will result in infection when injected into the skin (ulceroglandular/glandular tularemia) or inhaled (pneumonia). After inoculation into the skin, the organism multiplies locally; within 2 to 5 days (range, 1 to 10 days), it produces an erythematous, tender, or pruritic papule. The papule rapidly enlarges and forms an ulcer with a black base (chancriform lesion). The bacteria spread to regional lymph nodes, producing lymphadenopathy (buboes), and, with bacteremia, may spread to distant organs.

Tularemia is characterized by mononuclear cell infiltration with pyogranulomatous pathology. The histopathologic findings can be quite similar to those in tuberculosis, although tularemia develops more rapidly. As a facultatively intracellular bacterium, *F. tularensis* can parasitize both phagocytic and nonphagocytic host cells and survive intracellularly for prolonged periods. In the acute phase of infection, the primary organs affected (skin, lymph nodes, liver, and spleen) include areas of focal necrosis, initially surrounded by polymorphonuclear leukocytes (PMNs). Subsequently, granulomas form, with epithelioid cells, lymphocytes, and multinucleated giant cells surrounded by areas of necrosis. These areas may resemble caseation necrosis but later coalesce to form abscesses.

Conjunctival inoculation can result in infection of the eye, with regional lymph node enlargement (preauricular lymphadenopathy, Parinaud's complex). Aerosolization and inhalation or hematogenous spread of organisms can result in pneumonia. In the lung, an inflammatory reaction -- including foci of alveolar necrosis and cell infiltration (initially polymorphonuclear and later mononuclear) with granulomas -- develops. Chest roentgenograms usually reveal bilateral patchy infiltrates rather than large areas of consolidation. Pleural effusions are common and may contain blood. Lymphadenopathy occurs in regions draining infected organs. Therefore, in pulmonary infection, mediastinal adenopathy may be evident, while patients with oropharyngeal tularemia develop cervical lymphadenopathy. In gastrointestinal or typhoidal tularemia, mesenteric lymphadenopathy may follow the ingestion of large numbers of organisms. The term *typhoidal tularemia* may be used to describe severe bacteremic disease, irrespective of the mode of transmission or portal of entry. Meningitis has been reported as a primary or secondary manifestation of bacteremia. Patients may also present with fever and no

localizing signs.

## IMMUNOLOGY

Infection with *F. tularensis* stimulates the host to produce antibodies. However, this antibody response probably plays only a minor role in the containment of infection. In contrast, cell-mediated immunity, which develops over 2 to 4 weeks, plays a major role in containment and eradication of the infection. Macrophages, once activated, are capable of killing *F. tularensis*.

Immunospecific protection against tularemia can be afforded either by natural infection or by vaccination with live attenuated strains of *F. tularensis*. Killed vaccines, on the other hand, induce no protection against virulent *F. tularensis*. After natural infection or vaccination, serum antibodies to surface-exposed carbohydrate antigens predominate, whereas T cell determinants are located on membrane proteins beneath the bacterial capsule. T cell responses are thought to be due to priming by the organism. The anamnestic T cell response to *F. tularensis* seems to involve a multitude of microbial proteins, each with a distinct set of T cell determinants. A predominant role for CD4+ T cells is supported by the results of experiments in mice, which indicated that resistance to infection was restricted at the level of the MHC class II determinants. Humans primed to *F. tularensis* (like those primed to *Mycobacterium tuberculosis*) show a $T_H1$-like response. T cell proliferation is associated with the production of interleukin (IL) 2 and interferon g but with little or no production of IL-4.

Investigations of neutrophils in cases of tularemia have suggested thatPMNs are needed for defense against primary infection. PMNs may restrict the growth of *F. tularensis* before the organism becomes intracellular.

## CLINICAL MANIFESTATIONS

Tularemia often starts with a sudden onset of fever, chills, headache, and generalized myalgias and arthralgias (Table 161-1). This onset takes place when the organism penetrates the skin, is ingested, or is inhaled. An incubation period of 2 to 10 days is followed by the formation of an ulcer at the site of penetration (Fig. 161-CD1), with local inflammation. The ulcer may persist for several months as organisms are transported via the lymphatics to the regional lymph nodes. These nodes enlarge (Fig. 161-CD1) and may become necrotic and suppurative. If the organism enters the bloodstream, widespread dissemination as well as signs and symptoms of endotoxemia may result.

In the United States, most patients with tularemia (75 to 85%) acquire the infection by inoculation of the skin. In adults, the most common localized form is inguinal/femoral lymphadenopathy; in children, it is cervical lymphadenopathy. About 20% of patients develop a generalized maculopapular rash, which occasionally becomes pustular. Erythema nodosum occurs infrequently. The clinical manifestations of tularemia have been divided into various syndromes, which are listed inTable 161-2.

**Ulceroglandular/Glandular Tularemia** These two forms of tularemia account for approximately 75 to 85% of cases. The predominant form in children involves cervical or posterior auricular lymphadenopathy and is usually related to tick bites on the head and

neck. In adults, the most common form is inguinal/femoral lymphadenopathy resulting from insect and tick exposures on the lower limbs. In cases related to wild game, the usual portal of entry for *F. tularensis* is either an injury sustained while skinning or cleaning an animal carcass or a bite (usually on the hand). Epitrochlear lymphadenopathy/lymphadenitis is common in patients with bite-related injuries.

In ulceroglandular tularemia, the ulcer is erythematous, indurated, and nonhealing, with a punched-out appearance that lasts from 1 to 3 weeks. The papule may begin as an erythematous lesion that is tender or pruritic; it evolves over several days into an ulcer with sharply demarcated edges and a yellow exudate. The ulcer gradually develops a black base, and simultaneously the regional lymph nodes become tender and severely enlarged (Fig. 161-1). The affected lymph nodes may become fluctuant and drain spontaneously, but usually the condition resolves with effective treatment. Late suppuration of lymph nodes has been described in up to 25% of patients with ulceroglandular/glandular tularemia. Examination of material taken from these late fluctuant nodes after successful antimicrobial treatment has revealed sterile necrotic tissue. In 5 to 10% of patients, the skin lesion may be inapparent, with lymphadenopathy plus systemic signs and symptoms the only physical findings. This clinical syndrome is designated *glandular tularemia*. Conversely, a tick or deerfly bite on the trunk may result in an ulcer without evident lymphadenopathy.

**Oculoglandular Tularemia** In about 1% of patients, the portal of entry for *F. tularensis* is the conjunctiva. Usually, the organism reaches the conjunctiva through contact with contaminated fingers. The inflamed conjunctiva is painful, with numerous yellowish nodules and pinpoint ulcers. Purulent conjunctivitis with regional lymphadenopathy (preauricular, submandibular, or cervical) is evident. Because of debilitating pain, the patient may seek medical attention before regional lymphadenopathy develops. Painful preauricular lymphadenopathy is unique to tularemia and distinguishes it from cat-scratch disease, tuberculosis, sporotrichosis, and syphilis. Corneal perforation may occur.

**Oropharyngeal and Gastrointestinal Tularemia** Rarely, tularemia follows the ingestion of contaminated undercooked meat, the oral inoculation of *F. tularensis* from the hands in association with the skinning and cleaning of animal carcasses, or the consumption of contaminated food or water. Oral inoculation may result in acute, exudative, or membranous pharyngitis associated with cervical lymphadenopathy or in ulcerative intestinal lesions associated with mesenteric lymphadenopathy, diarrhea, abdominal pain, nausea, vomiting, and gastrointestinal bleeding. Infected tonsils become enlarged and develop a yellowish-white pseudomembrane, which can be confused with that of diphtheria. The clinical severity of gastrointestinal tularemia varies from mild, unexplained, persistent diarrhea with no other symptoms to a rapidly fulminant, fatal disease. In fatal cases, the extensive intestinal ulceration found at autopsy suggests an enormous inoculum.

**Pulmonary Tularemia** Tularemia pneumonia presents as variable parenchymal infiltrates that are unresponsive to treatment with b-lactam antibiotics. Tularemia must be considered in the differential diagnosis of atypical pneumonia in a patient with a history of travel to an endemic area. The disease can result from either inhalation of an infectious aerosol or spread to the lungs and pleura after bloodstream dissemination.

Inhalation-related pneumonia has been described in laboratory workers after exposure to contaminated materials and is associated with a relatively high mortality rate. Exposure to *F. tularensis* in aerosols from live domestic animals or dead wildlife (including birds) has been reported to cause pneumonia. Hematogenous dissemination to the lungs occurs in 10 to 15% of cases of ulceroglandular tularemia and in about half of cases of typhoidal tularemia. Previously, tularemia pneumonia was thought to be a disease of older patients, but as many as 10 to 15% of children with clinical manifestations of tularemia have parenchymal infiltrates detected by chest roentgenography. Patients with pneumonia usually have a nonproductive cough and may have dyspnea or pleuritic chest pain. Roentgenograms of the chest usually reveal bilateral patchy infiltrates (described as ovoid or lobar densities), lobar parenchymal infiltrates, and cavitary lesions. Pleural effusions may have a predominance of mononuclear leukocytes orPMNs and sometimes red blood cells. Empyema may develop. Patients with tularemia pneumonia can have blood cultures positive for *F. tularensis*.

**Typhoidal Tularemia** Once thought to represent up to 10% of all cases of tularemia, the typhoidal presentation is now considered rare in the United States. In this presentation, fever develops without apparent skin lesions or lymphadenopathy. In the absence of a history of possible contact with a vector, diagnosis can be extremely difficult. Blood cultures may be positive and patients may present with classic sepsis or septic shock in this acute systemic form of the infection. Typhoidal tularemia is usually associated with a huge inoculum or with a preexisting compromising condition. High continuous fevers, signs of endotoxemia, and severe headache are common findings. The patient may be delirious and may develop prostration and shock. If presumptive antibiotic therapy in culture-negative cases does not include an aminoglycoside, the mortality rate can approach 30%.

**Other Manifestations** *F. tularensis* infection has been associated with meningitis, pericarditis, hepatitis, peritonitis, endocarditis, osteomyelitis, and sepsis and septic shock with rhabdomyolysis and acute renal failure. In the rare cases of tularemia meningitis, a predominantly lymphocytic response is demonstrated in cerebrospinal fluid.

## DIFFERENTIAL DIAGNOSIS

When patients in endemic areas present with fever, chronic ulcerative skin lesions, and large tender lymph nodes, a diagnosis of tularemia should be made presumptively, and confirmatory diagnostic testing and appropriate therapy should be undertaken. When the possibility of tularemia is considered in a patient with this presentation in a nonendemic area, an attempt should be made to determine whether the individual has come into contact with a potential animal vector. The level of suspicion of tularemia should be especially high in hunters, trappers, game wardens, veterinarians, laboratory workers, and individuals with a history of exposure to an insect or another animal vector. However, up to 40%of patients with tularemia have no known history of epidemiologic contact with an animal vector.

The characteristic presentation of ulceroglandular tularemia does not pose a diagnostic problem, but a less classic progression of regional lymphadenopathy or glandular

tularemia must be differentiated from other diseases. The skin lesion may resemble those seen in sporotrichosis; skin infection with *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Mycobacterium marinum*; syphilis; anthrax; rat-bite fever (due to *Spirillum minus*); or rickettsiosis (scrub typhus). In the latter infections, regional lymphadenopathy is usually not as impressive as in tularemia. The lymphadenopathy of tularemia (especially glandular tularemia) must be differentiated from that of plague, lymphogranuloma venereum, and cat-scratch disease. In children, the differentiation from cat-scratch disease is made more difficult by the chronic papulovesicular lesion associated with *Bartonella henselae* infection (Chap. 163).

Oropharyngeal tularemia can resemble and must be differentiated from pharyngitis due to group A b-hemolytic streptococci, *Arcanobacterium haemolyticum*, or *Corynebacterium diphtheriae* as well as from infectious mononucleosis. Tularemia pneumonia may resemble any of the atypical pneumonias, including those due to various viruses, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *C. psittaci*, *Legionella pneumophila*, *Coxiella burnetii*, and (occasionally) *Histoplasma capsulatum.* Typhoidal tularemia may resemble typhoid fever, other *Salmonella* bacteremias, rickettsial infections (Rocky Mountain spotted fever, ehrlichiosis), brucellosis, infectious mononucleosis, acquired toxoplasmosis, miliary tuberculosis, sarcoidosis, and hematologic or reticuloendothelial malignancies.

## LABORATORY DIAGNOSIS

Direct microscopic examination of polychromatically stained tissue smears or clinical specimens reveals *F. tularensis* organisms, singly and in groups, both intra- and extracellularly. Gram's staining of clinical or biopsy material is of little value, as the small, weakly staining organisms cannot be readily distinguished from the background. An indirect fluorescent antibody test with commercially available antisera can be useful, although false-positive results due to *Legionella* spp. have been reported.

The diagnosis of tularemia is most frequently confirmed by serologic testing. In the standard tube agglutination test, a single titer of ³1:160 is interpreted as a presumptive positive result. A fourfold increase in titer between paired serum samples collected 2 to 3 weeks apart is considered diagnostic. False-negative serologic responses are obtained early in infection; up to 30% of patients infected for 3 weeks have sera that test negative. Late in infection, titers into the thousands are common, and titers of 1:20 to 1:80 may persist for years. A microagglutination test that may be as much as 100-fold more sensitive than the standard tube agglutination test has been described and is currently being used in many clinical microbiology laboratories. Enzyme-linked immunosorbent assays have proven useful for the detection of both antibodies and antigens. Analysis of urine for *F. tularensis* antigen has yielded promising results in clinical trials, but facilities for this type of analysis are not widely available. A skin test for delayed hypersensitivity to *F. tularensis* turns positive during the first week of illness and remains positive for years. The skin-test antigen, which is not commercially available, can boost titers of agglutinating antibody.

Culture and isolation of *F. tularensis* are difficult. In one study the organism was isolated in only 10% of more than 1000 human cases, 84% of which were confirmed by serology. The medium of choice is cysteine-glucose-blood agar. *F. tularensis* can be

isolated directly from infected ulcer scrapings, lymph-node biopsy specimens, gastric washings, sputum, and blood cultures. Colonies are blue-gray, round, smooth, and slightly mucoid. On media containing blood, a small zone ofa hemolysis usually surrounds the colony. Slide agglutination tests or direct fluorescent antibody tests with commercially available antisera can be applied directly to culture suspensions for identification.

The polymerase chain reaction (PCR) has been used to detect *F. tularensis* DNA. During a recent outbreak, a multiplex PCR was used to target 16S rRNA and to diagnose ulceroglandular tularemia with DNA extracted from wound swabs; the PCR result was positive in 29 (73%) of 40 serologically confirmed cases. However, this test has not been shown to be more sensitive than direct culture and at present remains a research tool.

## TREATMENT

*F. tularensis* cannot be subjected to standardized antimicrobial susceptibility testing because the organism will not grow on the media used. A wide variety of antibiotics, including all b-lactam antibiotics and the newer cephalosporins, are ineffective for the treatment of this infection. Several studies indicated that third-generation cephalosporins were active against *F. tularensis* in vitro, but clinical case reports suggested a nearly universal failure rate of ceftriaxone in pediatric patients with tularemia. Although in vitro data indicate that imipenem may be active, therapy with imipenem, sulfanilamides, and macrolides is not presently recommended because of the lack of relevant clinical data. Fluoroquinolones have shown promise in terms of their relatively low toxicity and their potential for oral administration. Chloramphenicol and tetracycline have been used successfully for treatment of the acute stages of tularemia but have been associated with higher relapse rates (up to 20%) than conventionally used agents.

Streptomycin, given intramuscularly at a dose of 7.5 to 10 mg/kg every 12 h, is considered the drug of choice for adults. In severe cases, 15 mg/kg every 12 h may be used for the first 48 to 72 h. Streptomycin is also considered the drug of choice for children; the appropriate dose is 30 to 40 mg/kg daily in two divided doses administered intramuscularly. In children, after a clinical response is demonstrated at 3 to 5 days, the dose can be reduced to 10 to 15 mg/kg daily in two divided doses. Therapy is typically continued for 7 to 10 days; however, in mild to moderate cases of tularemia in which the patient becomes afebrile within the first 48 to 72 h of streptomycin treatment, a 5- to 7-day course has been successful.

Gentamicin, at a dose of 1.7 mg/kg given intravenously or intramuscularly every 8 h, is also effective. The published experience in adults consists of two reports describing, respectively, nine and eight patients who were treated effectively with gentamicin. The eight patients in one of the reports all had fever before treatment, and all eight became afebrile within 24 to 72 h. In a recent pediatric study, other symptoms, such as tender lymphadenitis and pharyngitis, also responded within 24 to 72 h of the start of gentamicin therapy.

Virtually all strains of *F. tularensis* are susceptible to streptomycin and gentamicin. In

successfully treated patients, defervescence usually occurs within 2 days, but skin lesions and lymph nodes may take 1 to 2 weeks to heal. When therapy is not initiated within the first several days of illness, defervescence may be delayed. Relapses are uncommon with streptomycin or gentamicin therapy. Late lymph-node suppuration, however, occurs in approximately 40% of children, regardless of the treatment received. These nodes have typically been found to contain sterile necrotic tissue without evidence of active infection. Patients with fluctuant nodes should receive several days of antibiotic therapy before drainage to minimize the risk to hospital personnel. Unlike streptomycin and gentamicin, tobramycin is ineffective in the treatment of tularemia and should not be used.

## PROGNOSIS

If tularemia goes untreated, symptoms usually last 1 to 4 weeks but may continue for months. The mortality rate from severe untreated infection (including all cases of untreated tularemia pneumonia and typhoidal tularemia) can be as high as 30%. However, the overall mortality rate for untreated tularemia is<8%. Mortality is<1% with appropriate treatment. Poor outcomes are often associated with long delays in diagnosis and treatment. Lifelong immunity usually follows tularemia.

## PREVENTION

The prevention of tularemia is based on avoidance of exposure to biting and blood-sucking insects, especially ticks and deerflies. An intradermal vaccine made from live attenuated *F. tularensis* is available from the Centers for Disease Control and Prevention. This vaccine is effective in reducing the frequency and severity of infection. Vaccination of high-risk individuals working with large quantities of cultured organisms is recommended. Others who come into contact with the organisms, such as veterinarians, hunters, or game wardens, should consider vaccination, particularly if they live in endemic areas. The avoidance of skinning wild animals, especially rabbits, and the wearing of gloves while handling animal carcasses decrease the risk of transmission. Use of insect repellents and preparations that prevent tick attachment as well as prompt removal of ticks can be helpful. Prophylaxis of tularemia has not proved effective in patients with embedded ticks or insect bites. However, in patients who are known to have been exposed to large quantities of organisms (e.g., in the laboratory) and who have incubating infection with *F. tularensis*, early treatment can prevent the development of significant clinical disease.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 162. PLAGUE AND OTHER *YERSINIA* INFECTIONS - *Grant L. Campbell, David T. Dennis*

## PLAGUE

### DEFINITION

Plague is an acute, febrile, zoonotic disease caused by infection with *Yersinia pestis*. Although human cases are infrequent and are curable with antibiotics, plague is one of the most virulent and potentially lethal bacterial diseases known. The plague bacterium occurs in widely scattered foci in Asia, Africa, and the Americas, where its usual hosts are wild and peridomestic rodents. It is transmitted to humans typically by flea bite and less commonly by direct contact with infected animal tissues or by airborne droplet. The principal clinical forms of plague are bubonic, septicemic, and pneumonic. Although most cases are now sporadic, occurring singly or in small clusters, the potential for epidemic spread remains.

### ETIOLOGIC AGENT

*Y. pestis* is a gram-negative coccobacillus in the family Enterobacteriaceae. It is microaerophilic, nonmotile, nonsporulating, oxidase and urease negative, and biochemically unreactive. The organism is nonfastidious and infective for laboratory rodents. It grows well, if slowly, on routinely used microbiologic media (e.g., sheep blood agar, brain-heart infusion broth, and MacConkey agar). *Y. pestis* can multiply within a wide range of temperatures (-2°C to 45°C) and pH values (5.0 to 9.6), but optimal growth occurs at 28°C and at pH ~7.4. When incubated on agar plates at 37°C, colonies are pinpoint in size at 24 h and 1 to 2 mm in diameter at 48 h. The colonies are gray-white with irregular surfaces, described as having a "hammered-metal" appearance when viewed microscopically. In broth culture, *Y. pestis* grows without turbidity in clumps clinging to the sides of tubes. When stained with a polychromatic stain (e.g., Wayson or Giemsa), *Y. pestis* isolated from clinical specimens exhibits a characteristic bipolar appearance, often resembling closed safety pins. The bacterium is nonencapsulated but when grown at ³30°C produces a plasmid-expressed immunogenic envelope glycoprotein, fraction 1 (F1).

### HISTORIC BACKGROUND

Plague's deadly epidemic potential is notorious and well documented. The Justinian pandemic (542 to 767 A.D.) spread from central Africa to the Mediterranean littoral and thence to Asia Minor, causing an estimated 40 million deaths. The second pandemic began in central Asia, was carried to Sicily by ship from Constantinople in 1347, and swept through Europe and the British Isles in successive waves over the next four centuries. At its height, it killed as many as a quarter of the affected population and became known as the Black Death. In the third (modern) pandemic, plague appeared in Yunnan, China, in the latter half of the nineteenth century; established itself in Hong Kong in 1894; and spread by ship to Bombay in 1896 and subsequently to major port cities throughout the world, including San Francisco and several other West Coast and Gulf Coast ports in the United States. The plague bacillus was first cultured by Alexandre Yersin in Hong Kong in 1894. In 1898, Paul-Louis Simond, a French scientist

sent to investigate epidemic bubonic plague in Bombay, identified the bacillus in the tissues of dead rats and proposed transmission by rat fleas. Waldemar Haffkine, also in Bombay at that time, developed a crude vaccine.

By 1910, plague had circled the globe and established itself in rodent populations on all inhabited continents other than Australia. After 1920, however, the spread of plague was largely halted by international regulations that mandated control of rats in harbors and inspection and rat-proofing of ships. Before the third pandemic subsided, it resulted in an estimated 26 million plague cases and more than 12 million deaths, the vast majority in India. By 1950, plague outbreaks around the world had become isolated, sporadic, and manageable with modern techniques of surveillance, flea and rat control, and antimicrobial treatment of patients. Plague has nearly disappeared from cities and now occurs mostly in rural and semirural areas, where it is maintained in various rodents and their fleas. In the United States, the last outbreak of urban plague occurred in Los Angeles in 1924 and 1925, and human cases since then have resulted from animal plague exposures in rural areas of western states.

Because of its pandemic history, plague remains one of three quarantinable diseases subject to international health regulations (the other two being cholera and yellow fever). The alarm that plague is still able to evoke was highlighted by the public panic over an exaggerated international response to purported outbreaks of bubonic and pneumonic plague in India in 1994. The plague bacillus is considered to have a high potential for use in biologic terrorism; the agent is available around the world, has been "weaponized" for airborne delivery, and would be expected to cause a high primary fatality rate as well as secondary spread among an affected population.

## EPIDEMIOLOGY

*Y. pestis* is maintained in enzootic cycles involving relatively resistant wild rodents and their fleas in mostly remote, lightly populated areas of Asia, Africa, and the Americas and in limited rural foci in extreme southeastern Europe near the Caspian Sea. Humans and other nonrodent mammals are incidental hosts. Enzootic transmission places humans at low risk, and cases are typically infrequent and sporadic. Epizootic transmission involving susceptible rodents and efficient flea vectors (both are amplifying hosts) results in local or even widespread depopulation of susceptible rodents and poses a more serious threat to humans than does enzootic transmission. In the United States, the principal epizootic hosts are various ground squirrels, prairie dogs, and chipmunks; a variety of burrowing rodents act as epizootic hosts in rural areas elsewhere in the world. *Y. pestis* occasionally spills over from wild rodents to rat species that inhabit cultivated fields and adjacent homes, villages, and towns. The organism can then be transported from towns to cities by these highly adaptable rats and their fleas. Urban plague is currently reported sporadically from a few countries such as Vietnam, Myanmar, and Madagascar.

Plague in populated areas is most likely to develop when sanitation is poor and rats are numerous -- especially the common black or roof rat (*Rattus rattus*), its close relatives, and the larger brown sewer or Norway rat (*R. norvegicus*). A high mortality rate from plague in these susceptible rat populations forces their fleas to seek alternative hosts, including humans. The cosmopolitan oriental rat flea *Xenopsylla cheopis* and (in

southern Africa and Brazil) the related species *X. brasiliensis* are efficient vectors of the plague bacillus among rats and are also efficient vectors to humans. *Y. pestis* can multiply to enormous numbers in the foregut (proventriculus) of these fleas, resulting in a bolus of organisms and clotted blood that blocks the passage of subsequent blood meals. This situation occurs only at temperatures of£28°C and depends on a single protease expressed by the plasminogen activator (*pla*) gene of a 9.5-kb plasmid of *Y. pestis*. Regurgitation by a "blocked" flea while it feeds facilitates transmission of the plague bacillus to the new host.

Except for large outbreaks of pneumonic plague in Manchuria in the early part of the twentieth century, person-to-person respiratory transmission of plague during and since the third pandemic has occurred only sporadically and has been limited to clusters of close contacts of pneumonic plague patients, such as household members and caregivers. The 1994 outbreak of pneumonic plague in the city of Surat, India, although reported to be extensive, most likely involved fewer than 100 cases and 50 deaths; in 1998, a small outbreak of pneumonic plague occurred in the Ecuadoran Andes.

International health regulations require that national health authorities immediately report plague cases to the World Health Organization. From 1982 through 1996, 23,904 human plague cases and 2105 deaths (mortality, 9%) were reported by 24 countries. In the same 15-year period, the United States reported 212 plague cases (mean, 14 cases per year) and 27 deaths (mortality, 13%). Cases reported by the United States are confirmed by the plague laboratory of the Centers for Disease Control and Prevention (CDC). Animal plague occurs in 17 contiguous western states, extending from the Great Plains states and eastern Texas to the Pacific Coast; around 80% of human cases in this country now occur in New Mexico, Arizona, and Colorado and around 10% in California. Although plague in the United States is a rural disease, more than 50% of cases are thought to be caused by peridomestic exposures, especially in the southwestern states, where homes are often situated in natural surroundings that provide a favorable habitat for plague-susceptible animals (such as rock squirrels and wood rats) and their fleas. In the Sierra Nevadas of California and Nevada, epizootic plague in chipmunks and ground squirrels poses a risk to visitors in public parks. Hikers, campers, and hunters in natural areas throughout the western states are at a small but finite risk of exposure to plague, especially in the summer months.

Plague can be transmitted during the skinning and handling of carcasses of wild animals such as rabbits and hares, prairie dogs, wildcats, and coyotes. Such direct inoculation of mammal-adapted organisms is associated with primary septicemia and high mortality. Oropharyngeal plague can result from the ingestion of undercooked contaminated meat and perhaps from the manual transfer of infected fluids to the mouth during the handling of infected animal tissues.

Carnivores, including dogs and cats, can become infected with *Y. pestis* by eating infected rodents and perhaps by being bitten by fleas from infected rodents. Although clinical plague commonly develops in infected cats, it rarely does so in infected dogs, which thus do not directly expose humans to infection. However, both dogs and cats may transport infected fleas from rodent-infested areas to the home environment.

From 1950 through 1996, 387 plague cases were reported in the United States. Of the

376 evaluable cases, 322 cases (86%) presented as primary lymphadenitic (bubonic) plague, almost all of them thought to be associated with flea bites; 46 cases (12%) presented as primary septicemic plague, many of them following direct animal exposures; and 8 cases (2%) presented as primary pneumonic plague, 6 resulting from the inhalation of respiratory droplets released by infected cats and 2 from unknown sources. The last case of human-to-human plague transmission in the United States occurred in the Los Angeles outbreak of 1924/1925.

## PATHOGENESIS AND PATHOLOGY

*Y. pestis* is highly invasive and pathogenic. The mechanisms by which the organism causes disease are incompletely understood, but both chromosome- and plasmid-encoded gene products as well as altered cell-mediated immune responses are probably involved. Three plasmids encode for a variety of known or presumed virulence factors, including the F1 envelope antigen, which confers bacterial resistance to phagocytosis by polymorphonuclear leukocytes (PMNs) in vitro; a murine exotoxin; the V antigen, which is essential for virulence, may immunocompromise the host by suppressing the synthesis of interferon g and tumor necrosis factor a, and stimulates protective immunity in laboratory animals; pesticin, a bactericidal protein of unknown function and importance; a protease that can activate plasminogen and degrade serum complement and that is thought to play a role in the dissemination of *Y. pestis* from peripheral sites of infection; a coagulase; and a fibrinolysin. A lipopolysaccharide endotoxin, believed to be chromosomally encoded, is probably important in triggering the systemic inflammatory response syndrome and its complications.

*Y. pestis* organisms inoculated through the skin or mucous membranes usually invade superficial lymphatic vessels and are carried to regional lymph nodes, although direct bloodstream inoculation may take place. Mononuclear phagocytes, which can phagocytize *Y. pestis* organisms without destroying them, may play a role in dissemination of the infection to distant sites. Plague can involve almost any organ, and untreated plague generally results in widespread and massive tissue destruction. In the early stages, infected lymph nodes (buboes,Fig. 162-1) are characterized by edema and congestion without inflammatory infiltrates or apparent vascular injury. Fully developed buboes contain huge numbers of infectious plague organisms and show distorted or obliterated lymph node architecture with vascular destruction and hemorrhage, serosanguineous effusion, necrosis, and a mild neutrophilic infiltration. At this stage, the effusion often involves perinodal tissues. If several adjacent lymph nodes are involved, a boggy edematous mass can result.

Primary septicemic plague results from the direct inoculation of bacteria from infected fluids or tissues or from an infective flea bite in the apparent absence of a bubo; secondary septicemic plague occurs when lymphatic and other host defenses are breached and the plague bacillus multiplies within the bloodstream. In fatal septicemic plague, multifocal hepatic and splenic necrosis is common. Diffuse interstitial myocarditis with cardiac dilatation is sometimes found. If disseminated intravascular coagulation (DIC) ensues, vascular necrosis may lead to widespread cutaneous, mucosal, and serosal ecchymoses and petechiae. Acral gangrene sometimes develops.

Primary plague pneumonia generally begins as a lobular process and then extends by

confluence, becoming lobar and then multilobar (Fig. 162-2). Plague organisms are typically most numerous in the alveoli. Secondary plague pneumonia begins more diffusely, with organisms usually most numerous in the interstitium. In untreated cases of both primary and secondary plague pneumonia, diffuse pulmonary hemorrhage, necrosis, and neutrophilic infiltration develop.

## MANIFESTATIONS

Plague is characterized by a rapid onset of fever and other systemic manifestations of gram-negative bacterial infection. If it is not quickly and correctly treated, plague can follow a toxic course, resulting in shock, multiple-organ failure, and death. In humans, the three principal forms of plague are bubonic, septicemic, and pneumonic. Bubonic plague, the most common form, is almost always caused by the bite of an infected flea but occasionally results from direct inoculation of infectious fluids. Septicemic and pneumonic plague can be either primary or secondary to metastatic spread. Unusual secondary forms include plague meningitis, endophthalmitis, and lymphadenitis at multiple sites. Primary plague pharyngitis has been documented by culture of organisms from throat swabs and can result from respiratory exposure or ingestion of contaminated meat.

Bubonic plague usually has an incubation period of 2 to 6 days, occasionally longer. Typically, the patient experiences chills; fever, with temperatures that rise within hours to³38°C; myalgias; arthralgias; headache; and a feeling of weakness. Soon -- usually within 24 h -- the patient notices tenderness and pain in one or more regional lymph nodes proximal to the site of inoculation of the plague bacillus (Fig. 162-1). Because fleas often bite the legs, femoral and inguinal nodes are most commonly involved; axillary and cervical nodes are next most commonly affected. The enlarging bubo becomes progressively painful and tender, sometimes exquisitely so. The patient usually guards against palpation and limits movement, pressure, and stretch around the bubo. The surrounding tissue often becomes edematous, sometimes markedly so, and the overlying skin may be erythematous, warm, and tense. Inspection of the skin surrounding or distal to the bubo sometimes reveals the site of a flea bite marked by a small papule, pustule, eschar, or ulcer. A list of lymphadenitic conditions that could be confused with a plague bubo would include *Staphylococcus aureus* and group A b-hemolytic streptococcal infections, cat-scratch disease, and tularemia. The bubo of plague is distinguishable from lymphadenitis of most other causes, however, by its rapid onset, its extreme tenderness, the accompanying signs of toxemia, and the absence of cellulitis or obvious ascending lymphangitis.

Treated in the uncomplicated state with an appropriate antibiotic, bubonic plague usually responds quickly, with defervescence and alleviation of other systemic manifestations over 2 to 5 days. Buboes often remain enlarged and tender for a week or more after the initiation of treatment and can become fluctuant. Without effective antimicrobial treatment, patients with typical bubonic plague manifest an increasingly toxic state of fever, tachycardia, lethargy leading to prostration, agitation and confusion, and (occasionally) convulsions and delirium. Secondary plague sepsis may result in an alarmingly rapid and refractory cascade ofDIC, bleeding, shock, and organ failure. Mild forms of bubonic plague, called *pestis minor*, have been described in South America and elsewhere; in these cases, the patients are ambulatory, are only mildly febrile, and

have subacute buboes.

Septicemic plague is a progressive, overwhelming bacterial infection. Primary septicemia develops in the absence of apparent regional lymphadenitis, and the diagnosis of plague is often not suspected until preliminary blood culture results are reported to be positive by the laboratory. *Y. pestis*, however, can also be cultured from the blood of most bubonic plague patients, and bacteremia should be distinguished from septicemia, in which the patient is desperately ill and requires aggressive care. Patients with septicemic plague often present with gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain, which may further confound the correct diagnosis. If not treated early with appropriate antibiotics, septicemic plague can be fulminant and fatal. In the United States in 1950 through 1996, 66 cases of septicemic plague and 18 deaths were reported, for a case-fatality rate of 27%. Petechiae, ecchymoses, bleeding from puncture wounds and orifices, and gangrene of acral parts are manifestations ofDIC; refractory hypotension, renal shutdown, obtundation, and other signs of shock are preterminal events. Adult respiratory distress syndrome (ARDS), which can occur at any stage of septicemic plague, is sometimes confused with other conditions, such as hantavirus pulmonary syndrome.

Of all forms of the disease, pneumonic plague develops most rapidly and is most frequently fatal. The incubation period for primary pneumonic plague is rarely longer than 1 to 4 days. The onset is most often sudden, with chills, fever, headache, myalgias, weakness, and dizziness. Pulmonary signs, including cough, sputum production, chest pain, tachypnea, and dyspnea, typically arise on the second day of illness and may be accompanied by hemoptysis, increasing respiratory distress, cardiopulmonary insufficiency, and circulatory collapse. In primary plague pneumonia, the sputum is most often watery or mucoid, frothy, and blood-tinged, but it may become frankly bloody. Pulmonary signs in primary pneumonic plague may indicate involvement of a single lobe in the early stage, with rapidly developing segmental consolidation before bronchopneumonic spread to other lobes of the same and opposite lungs. Liquefaction necrosis and cavitation may occur early in areas of consolidation and may or may not leave significant residual scarring.

Secondary plague pneumonia manifests first as diffuse interstitial pneumonitis in which sputum production is scant; since the sputum is more likely to be inspissated and tenacious in character than the sputum found in primary pneumonia, it may be less infectious. In the United States in 1950 through 1996, 39 cases of secondary pneumonic plague and 8 cases of primary pneumonic plague were reported, with no known transmission to contacts and an overall case-fatality rate of 41%. Observers in the early twentieth century remarked on the relative lack of auscultatory findings, the usual presence of toxemia, and the frequency of sudden death in patients with pneumonic plague as compared to patients with other bacterial pneumonias.

Meningitis is an unusual manifestation of plague. In the United States, there were 12 meningitis cases among the 376 evaluable plague cases reported in 1950 through 1996. All cases of meningitis were complications of bubonic plague, and all patients survived. Although meningitis may be a part of the initial presentation of plague, its onset is often delayed and is a manifestation of insufficient treatment. Recent cases in the United States have occurred during the first and second weeks of antibiotic

treatment for bubonic plague. Chronic relapsing meningeal plague over periods of weeks or even months was described in the preantibiotic era. The affected patients typically presented with fever, headache, meningismus, and pleocytosis.

Plague pharyngitis presents as fever, sore throat, cervical lymphadenitis, and headache and is often indistinguishable clinically from pharyngitis of other infectious etiologies. Caregivers working in plague-endemic areas must be alert to the possibility of plague to avoid misdiagnosis leading to delayed and/or inappropriate treatment.

## LABORATORY FINDINGS AND DIAGNOSIS

Since plague is a rare disease in the United States, a high index of clinical suspicion as well as the elicitation of a thorough clinical and epidemiologic history and a careful physical examination are required for timely diagnosis and prompt institution of specific therapy. When the diagnosis of plague is delayed or missed altogether, a high case-fatality rate results; infected travelers who seek medical care after they have left endemic areas (peripatetic plague cases) are at especially high risk. Plague must be considered in the differential diagnosis of sepsis in an otherwise-healthy person who has a history of recent travel to or residence in the rural western United States. When the diagnosis of plague is being considered, close communication between clinicians and the diagnostic laboratory and between the diagnostic laboratory and a qualified reference laboratory is essential. Tests for plague are highly reliable when conducted by laboratory personnel experienced with *Y. pestis*, but such expertise is usually limited to selected reference laboratories, including state health department laboratories in some plague-endemic states and theCDCplague laboratory (Fort Collins, Colorado; tel. 970-221-6400).

When plague is suspected, specimens should be collected promptly for laboratory studies, chest roentgenograms should be obtained, and specific antimicrobial therapy should be initiated pending confirmation. Appropriate diagnostic specimens for smear and culture include citrated or heparinized whole blood from all patients with suspected plague, bubo aspirates from those with suspected buboes, sputum samples or tracheal aspirates from those with suspected pneumonic plague, and cerebrospinal fluid (CSF) from those with suspected plague meningitis. Since early buboes are often exquisitely tender and are seldom fluctuant or necrotic, these lesions usually require aspiration under local anesthesia following the injection of 1 to 2 mL of normal saline (sterile but nonbacteriostatic) into the bubo with a 20- to 22-gauge needle. A variety of appropriate culture media (including brain-heart infusion broth, sheep blood agar, and MacConkey agar) should be inoculated with a portion of each specimen. Moreover, for each specimen, at least one smear should be examined immediately with Wayson or Giemsa stain and at least one with Gram's stain; a smear should also be submitted for direct fluorescent antibody testing. An acute-phase serum specimen should be tested for antibody to *Y. pestis*; whenever possible, a convalescent-phase serum specimen collected 3 to 4 weeks later should also be tested. When a patient dies and plague is suspected, appropriate autopsy tissues for culture, direct fluorescent antibody testing, and immunohistochemical staining include buboes, all solid organs (especially liver, spleen, and lung), and bone marrow. If culture of such specimens is to be attempted, they should be sent to the laboratory either fresh or frozen on dry ice, not in preservatives or fixatives. If necessary, Cary-Blair or a similar medium can be used to

transport *Y. pestis*-infected tissues.

Laboratory confirmation of plague depends on the isolation of *Y. pestis* from cultures of body fluids or tissues. Cultures of three blood samples taken over a 45-min period before treatment will usually result in isolation of the bacterium. *Y. pestis* strains are readily distinguished from those of the closely related species *Y. pseudotuberculosis* by differences in biochemical profile, temperature-dependent susceptibility to lysis by a *Y. pestis*-specific bacteriophage, and motility. Automated bacteriologic test systems can be used to assist in the identification of isolates as *Y. pestis*, but *Y. pestis* can be misidentified (e.g., as *Y. pseudotuberculosis*) or overlooked if these systems are improperly programmed.

In the absence of *Y. pestis* isolation, plague cases can be confirmed either by the demonstration of seroconversion (a fourfold or greater titer rise) to *Y. pestis* F1 antigen in passive hemagglutination tests of acute- and convalescent-phase serum specimens or by detection of an antibody titer of>128 in a single serum sample from a patient with a plague-compatible illness who has not received plague vaccine. The specificity of a positive passive-hemagglutination test requires confirmation with the F1 antigen hemagglutination-inhibition test. A few plague patients seroconvert to F1 antigen as early as 5 days after the onset of illness. Most seroconvert between 1 and 2 weeks after onset; a few seroconvert 3 weeks or more after onset; and a few (<5%) fail to seroconvert at all. Early, specific antibiotic treatment may delay seroconversion by several weeks. After seroconversion, positive serologic titers diminish gradually over months to years. Enzyme-linked immunosorbent assays (ELISAs) for IgM and IgG antibodies to *Y. pestis* are replacing hemagglutination tests in some laboratories. Other new test methods include IgM antibody capture and competitive blocking for detection of antibody to F1.

Detection of F1 antigen in tissues or fluids by direct fluorescent antibody testing or by antigen capture is presumptive evidence of plague, as is an F1 antibody titer of>10 in a single serum sample from a patient with a plague-compatible illness who has not received plague vaccine. Visualization of characteristic bipolar bacilli in a Giemsa- or Wayson-stained smear constitutes supportive evidence of plague. Tularemia, especially the glandular, typhoidal, and pneumonic forms, can sometimes be confused clinically and epidemiologically with plague, but the results of microbiologic and serologic tests should readily distinguish these two diseases.

Patients with plague typically have white blood cell (WBC) counts of 15,000 to 25,000/uL, with a predominance ofPMNs and a left shift. Leukemoid reactions with WBC counts as high as 100,000/uL can occur. Modest thrombocytopenia is usually documented, and fibrin-fibrinogen split products are often detected even in patients without frankDIC. Serum levels of aminotransferases and bilirubin may be elevated. Chest roentgenograms of patients with pneumonic plague usually show patchy bronchopneumonic infiltrates as well as lobar or segmental consolidation with or without confluence (Fig. 162-2); they occasionally show cavitation. Stained sputum samples usually contain PMNs and characteristic bipolar-staining bacilli. In *Y. pestis* septicemia, visualization of the characteristic bacilli in a routine blood smear or a buffy-coat smear is an uncommon but grave prognostic sign (Fig. 162-3). In patients with plague meningitis, pleocytosis with a predominance of PMNs is the rule, and the characteristic bacilli are

usually visible in stainedCSFsmears.

## TREATMENT

Left untreated, plague is fatal in more than 50% of cases of bubonic disease and in nearly all cases of septicemic and pneumonic disease. The overall mortality rate for plague cases in the United States since 1950 has been ~16%; deaths are almost always due to delays in seeking treatment, misdiagnosis, delays in the institution of treatment, or incorrect treatment. Rapid diagnosis and appropriate antimicrobial therapy are essential.

Guidelines for the treatment of plague are given in Table 162-1. Although streptomycin is the drug of choice, gentamicin is increasingly used for the treatment of plague in the United States because of its ready availability; it is probably as effective as streptomycin, although results of controlled studies in humans have not been published. Alternative antibiotics include the tetracyclines and chloramphenicol; these agents are usually given orally with initial loading doses but may be given intravenously to critically ill patients and to patients unable to tolerate oral medication. Penicillins, cephalosporins, and macrolides are suboptimal and should not be used. Doxycycline may be as effective as other tetracyclines or even more so, but comparative evaluations have not been made. Trimethoprim-sulfamethoxazole has been used successfully to treat bubonic plague but is not considered a first-line choice. Chloramphenicol is indicated for the treatment of plague meningitis, pleuritis, endophthalmitis, and myocarditis because of its superior tissue penetration; it is used alone or in combination with streptomycin. In general, antimicrobial treatment should be continued for 10 days or for at least 3 days after the patient has become afebrile and has made a clinical recovery. Patients initially given intravenous antibiotics may be switched to oral regimens upon clinical improvement. Such improvement is usually evident 2 or 3 days after the start of treatment, even though fever may continue for several days.

Consequences of delayed treatment of plague includeDIC,ARDS, and other complications of gram-negative sepsis. Patients with these disorders require intensive monitoring and close physiologic support, as outlined elsewhere (Chaps. 117 and265). Buboes may require surgical drainage. Abscessed nodes can cause recurrent fever in patients who have apparently recovered; this relation may be occult if intrathoracic or intraabdominal nodes are involved. Although *Y. pestis* is considered to be genetically stable, a multidrug-resistant strain was isolated from a plague patient in Madagascar. This strain exhibited resistance (mediated by a transferable plasmid) to all first-line antibiotics used for treatment of plague and to the principal alternatives used for treatment and prophylaxis.

## PREVENTION AND CONTROL

Persons at greatest risk for plague in the United States are those who live, work, and participate in outdoor recreational activities in areas of those western states in which plague is enzootic. Surveillance, education, and environmental management are the cornerstones of prevention and control. A network of biologists and public health specialists coordinates these activities through local and state health departments and theCDC. Personal protective measures include the avoidance of areas with known

epizootic plague (which may be posted) and of sick or dead animals; the use of repellents, insecticides, and protective clothing when at risk of exposure to rodents' fleas; and the wearing of gloves when handling animal carcasses. Short-term antibiotic prophylaxis (Table 162-2) is recommended for persons known to have had direct contact with a patient with suspected or confirmed pneumonic plague and occasionally for persons who are unable to avoid an area where a plague outbreak is in progress or who may be caring for patients with plague. Patients in whom plague is suspected should be managed under isolation precautions for respiratory droplet transmission until pneumonia has been ruled out or until 48 h of specific antimicrobial therapy has been administered, after which universal precautions are adequate.

Rodent food (garbage, pet food) and habitats (brush piles, junk heaps, woodpiles) should be eliminated in domestic, peridomestic, and working environments; buildings and food stores should be rodent-proofed. The control of fleas with insecticides is a key public health measure in situations where epizootic plague activity places humans at high risk; this effort includes dusting and spraying of rodent burrows, rodent runs, and other sites where rodents and their fleas are found. In plague-endemic areas of the western United States, persons should keep their dogs and cats free of fleas and restrained. The decision to control plague by killing rodents should be left to public health authorities, and such a program should be carried out only in conjunction with effective flea control. Killing of rodents has no lasting benefit without environmental sanitation.

The previously used killed, whole-cell plague vaccine is no longer manufactured in the United States. Efforts are being made to develop improved vaccines in which the production of specific immunoprotective antibodies to *Y. pestis* is induced by recombinant antigens. In the United States, the indications for use of these newer vaccines would probably be similar to those for the previously available killed vaccine, which was mostly limited to protecting laboratory personnel who routinely worked with *Y. pestis* and some persons whose vocations brought them into regular contact with wild rodents and their fleas in areas with enzootic or epizootic plague. In addition, a vaccine might be useful in protecting selected military personnel and in responding to the possible use of *Y. pestis* as a weapon of bioterrorism.

## OTHER *YERSINIA* INFECTIONS

### DEFINITION

Yersiniosis is an uncommon bacterial zoonosis caused by infection with either of the two enteropathogenic *Yersinia* species: *Y. enterocolitica* or *Y. pseudotuberculosis*. Reservoir hosts of these bacteria include swine and other wild and domestic animals. These yersiniae are transmitted to humans predominantly via the oral route. Both sporadic cases and common-source outbreaks occur. The most frequent acute clinical manifestations are (1) enteritis or enterocolitis with self-limited diarrhea (especially with *Y. enterocolitica*), and (2) mesenteric adenitis and terminal ileitis (especially with *Y. pseudotuberculosis*), which can be difficult to distinguish from acute appendicitis. Septicemia and metastatic focal infections are less common. Some cases of yersiniosis are complicated by nonsuppurative, extraintestinal, inflammatory sequelae -- e.g., reactive arthritis (Chap. 315) and erythema nodosum (Chap. 18).

## ETIOLOGIC AGENTS

*Y. enterocolitica* and *Y. pseudotuberculosis* are pleomorphic gram-negative bacilli in the family Enterobacteriaceae. They are aerobic or facultatively anaerobic, motile at 25°C, nonmotile at 37°C, oxidase negative, urease positive, able to ferment glucose, unable to ferment lactose, and usually able to reduce nitrates. They grow well, if slowly, on nonselective media (e.g., blood agar) and on most of the routine media used to select for enteric bacteria (e.g., MacConkey agar). They can multiply within a wide temperature range (-1°C to 45°C). The most clinically and epidemiologically useful methods for identifying pathogenic *Y. enterocolitica* isolates are biotyping based on biochemical profiles and serotyping according to somatic O and H antigens. Six biotypes and more than 60 serotypes of *Y. enterocolitica* are recognized. A separate serotyping system for *Y. pseudotuberculosis* (also based on somatic antigens) has distinguished six major serotypes (I through VI) and their subtypes.

## EPIDEMIOLOGY

*Y. enterocolitica* is distributed worldwide and has been isolated from soil, fresh water, contaminated foodstuffs (e.g., meat, milk, and vegetables), and a wide variety of wild and domestic animals, including mammals, birds, amphibians, fish, and shellfish. Many serotypes isolated from environmental sources, however, evidently are not human pathogens. Most human infections have been caused by *Y. enterocolitica* serotypes O:3, O:5, O:8, and O:9, which are primarily associated with wild and domestic mammals. The incidence of these infections and their sequelae is highest in Scandinavia and some other northern European countries, but this observation may be in part an artifact of underrecognition in other countries. Because many individuals with enteric *Y. enterocolitica* infection are asymptomatic or minimally symptomatic and do not seek medical attention, reliable population-based estimates of incidence are unavailable. However, in many clinical microbiology laboratories in recent decades, *Y. enterocolitica* has been the fourth most common bacterial pathogen isolated from patients' fecal specimens, trailing *Salmonella* (the most frequently isolated), *Campylobacter*, and *Shigella* species.

All age groups are susceptible to *Y. enterocolitica* infections, but the majority of cases of enterocolitis are in children aged 1 to 4. Moreover, these infections show a modest predilection for males. Mesenteric adenitis and terminal ileitis are most common among older children and young adults. Risk factors for *Y. enterocolitica* septicemia and metastatic focal infections include chronic liver disease, malignancy, diabetes mellitus, immunosuppressive therapy, alcoholism, malnutrition, advanced age, iron overload (see below), and hemolytic anemias (including the thalassemias). The nonsuppurative sequelae of yersiniosis are most common among adults. HLA-B27 is expressed in 70 to 80% of patients who develop reactive arthritis associated with yersiniosis. HLA-B27 is not a risk factor for *Yersinia*-induced erythema nodosum; females with this condition outnumber males by 2 to 1. In Europe, *Y. enterocolitica* infections are more common in the cooler months than in warmer weather. In North America, no consistent seasonal pattern has been documented.

For several decades, serotypes O:3 and O:9 have predominated among *Y.*

*enterocolitica* isolates from patients in Europe. Serotype O:3 has also predominated in Canada and Japan. In the United States, serotype O:3 emerged in the 1980s to surpass serotype O:8 in frequency of isolation from patients. The incidence of *Yersinia*-induced nonsuppurative sequelae reportedly is 10 to 30% in Scandinavia and much lower in most other countries, including the United States. No convincing explanation for this observation has been confirmed, but reasonable possibilities include population genetic factors and geographic strain variation.

Common-source outbreaks of *Y. enterocolitica* enteritis have been traced to such vehicles as raw milk, contaminated pasteurized milk, and foods prepared with contaminated fresh water. In Belgium, the ingestion of ground raw pork (a regional custom) is a significant risk factor for sporadic infection with *Y. enterocolitica* serotypes O:3 and O:9. These serotypes commonly colonize the oral cavity and intestines of European swine, and *Y. enterocolitica* infection is an occupational risk of swine butchers in Europe. In the United States, sporadic cases and one outbreak of *Y. enterocolitica* O:3 infection have been associated with the preparation or ingestion of raw pork intestines (chitterlings). In some cases of yersiniosis, circumstantial evidence suggests transmission via contact with dogs and cats or their feces. Several nosocomial outbreaks of *Y. enterocolitica* infection have been described; fecal-oral transmission from person to person was suspected. Fecal-oral transmission among family members may also explain occasional secondary cases in households. In a prospective study of 50 children with *Y. enterocolitica* enteritis, fecal excretion of the organism persisted for an average of 27 days (range, 4 to 79 days) after the cessation of symptoms. A chronic carrier state, however, has not been demonstrated. *Y. enterocolitica* is a rare but often lethal cause of transfusion-associated septicemia. The explanation is that blood donors occasionally have transient, occult *Y. enterocolitica* bacteremia and that this organism can slowly multiply to high concentrations in blood refrigerated for at least 10 to 20 days.

The ecology of *Y. pseudotuberculosis* seems to parallel that of *Y. enterocolitica* closely. *Y. pseudotuberculosis* is also widespread in wild and domestic animals and is isolated from many environmental sources. Human infections with *Y. pseudotuberculosis*, however, appear to be rare. In North America and Europe, most such infections have been with serotype I, but outbreaks involving other serotypes have occurred in Japan and Scandinavia. Swine appear to be an important reservoir for pathogenic strains of *Y. pseudotuberculosis*.

## PATHOGENESIS AND PATHOLOGY

Except in rare instances of transmission via contaminated blood products or direct cutaneous inoculation, the enteropathogenic yersiniae are thought to enter the host via the oral route. The 50% infectious dose in humans is uncertain but may be $^{3}10^{9}$. The incubation period averages 5 days (range, 1 to 11 days). Studies of animals have shown that the organisms initially invade the ileal epithelium, then are translocated via M cells into the lamina propria, and finally enter Peyer's patches, where they are able to replicate. They subsequently drain into the mesenteric lymph nodes, which undergo hyperplasia and from which the bacteria can be distributed systemically. The mesenteric lymph nodes can become intensely swollen and matted and are occasionally detected on physical examination as a tender right lower quadrant mass. Intestinal inflammation (most commonly of the distal ileum and less commonly of the ascending colon)

develops and may be accompanied by mucosal ulcerations and by the shedding ofPMNs and red blood cells into the intestinal lumen. In relatively severe cases, thrombosis of mesenteric blood vessels, intestinal hemorrhage, and necrosis can occur. In patients with enteropathogenic yersinial infections who undergo exploratory laparotomy, the appendix usually is histologically normal or shows only lymphoid hyperplasia, but frank suppuration is sometimes evident.

A plasmid of ~70 kb is essential for virulence of the enteropathogenic yersiniae because it encodes at least six *Yersinia* outer-membrane proteins, some of which confer to bacterial strains such properties as cytotoxicity; resistance to phagocytosis byPMNs; and the abilities to cause monocyte apoptosis (programmed cell death), to suppress the host's expression of tumor necrosis factora, to interfere with platelet aggregation and host complement activation, and to dephosphorylate host proteins. A chromosomal gene (*inv*) encodes for the surface protein invasin, which is necessary for yersinial invasion of nonphagocytic host cells (e.g., epithelial cells) in vitro and which facilitates the translocation of bacteria across the intestinal epithelium. Both *Y. enterocolitica* and *Y. pseudotuberculosis* can express at least one protein superantigen that selectively stimulates the proliferation of T cells. Many strains of *Y. enterocolitica* produce a heat-stable enterotoxin that is similar to *Escherichia coli* enterotoxin. The cell walls of *Y. enterocolitica* and *Y. pseudotuberculosis* contain a lipopolysaccharide (endotoxin). The roles of superantigens, enterotoxin, and endotoxin in the pathogenesis of yersiniosis are unclear. Some *Yersinia* strains are unable to synthesize bacterial iron chelators called *siderophores*. However, they can exploit host-chelated iron stores and the drug deferoxamine (a siderophore produced by *Streptomyces pilosus*). Therefore, iron overload (e.g., caused by hemodialysis or multiple transfusions) and deferoxamine therapy appear to be independent risk factors for *Y. enterocolitica* bacteremia (especially that involving serotypes O:3 and O:9) and to a lesser degree for *Y. pseudotuberculosis* bacteremia.

Immunogenetic factors and cell-mediated immune responses are clearly involved in the pathogenesis of reactive arthritis following infection with the enteropathogenic yersiniae. As noted above, most patients with *Yersinia*-induced reactive arthritis express HLA-B27. In addition, *Y. pseudotuberculosis* shares at least one cross-reactive epitope with HLA-B27, and *Y. enterocolitica* infection alters the expression of serologic HLA-B27 epitopes on lymphocytes and monocytes. In patients with reactive arthritis following *Y. enterocolitica* infection, yersinial antigens are commonly detectable in synovial fluid cells in the apparent absence of whole organisms. Thus, it is unknown whether the arthritis results from occult bacterial persistence through self-tolerance of HLA-B27 with a failure of cross-reactive immune responses to yersiniae, from an immune response to common antigenic determinants shared by the bacteria and host HLA-B27 (i.e., molecular mimicry), or from other mechanisms. The pathogenesis of *Yersinia*-induced erythema nodosum is obscure.

In some assays, patients with Graves' disease have an increased prevalence of serum antibodies to *Y. enterocolitica*, and the immunoglobulins of patients recovering from *Y. enterocolitica* infections react with the human thyroid-stimulating hormone receptor. However, a link between *Y. enterocolitica* infection and the subsequent development of autoimmune thyroiditis has not been convincingly demonstrated.

## MANIFESTATIONS

The principal clinical manifestations of *Y. enterocolitica* infection are enteritis, enterocolitis, mesenteric adenitis, and terminal ileitis. Less common manifestations include exudative pharyngitis, septicemia, metastatic focal infections, reactive polyarthritis, and erythema nodosum. When age groups are combined, the most common presentation of *Y. enterocolitica* infection is acute diarrhea from enteritis or enterocolitis. Low-grade fever and cramping abdominal pain occur in most cases, nausea and vomiting in 15 to 40%, hematochezia in up to 30%, and a generalized maculopapular skin rash in a few cases. Diarrhea persists for an average of 2 weeks (range, 1 day to many months), during which the frequency of bowel movements diminishes. Uncommonly, enteritis or enterocolitis can be complicated by severe abdominal pain and high fever. Rare (and sometimes fatal) complications include diffuse inflammation, ulceration, hemorrhage, and necrosis of the small bowel and colon; intestinal perforation; peritonitis; ascending cholangitis; mesenteric vein thrombosis; diverticulitis; toxic megacolon; and ileocecal intussusception.

The syndrome of mesenteric adenitis and terminal ileitis without diarrhea is easily confused with appendicitis. Low-grade fever and right lower quadrant pain, tenderness, guarding, and rebound tenderness are common. During six recognized common-source outbreaks in the United States, 10% of 444 patients with symptomatic undiagnosed *Y. enterocolitica* infections underwent laparotomy for suspected appendicitis; surgical incisions became infected with *Y. enterocolitica* in a few of these cases.

Acute pharyngitis and pharyngotonsillitis, with or without cervical adenitis or intestinal illness, are less common but potentially lethal manifestations of *Y. enterocolitica* infection, particularly in adults. *Y. enterocolitica* septicemia generally presents as a severe illness with fever and leukocytosis, often with abdominal pain and jaundice and without localized signs of infection. Metastatic focal *Y. enterocolitica* infections can occur with or without clinically apparent bacteremia and can affect almost any organ system. Examples include abscess formation (e.g., in liver, spleen, kidney, lung, skeletal muscle, lymph node, or cutaneous tissue), osteomyelitis, meningitis, peritonitis, urinary tract infection, pneumonia, empyema, endocarditis, pericarditis, mycotic aneurysm, septic arthritis, suppurative conjunctivitis, panophthalmitis, Parinaud's oculoglandular syndrome, and cutaneous pustules or bullae.

In Scandinavia, the incidence of reactive arthritis following *Y. enterocolitica* infection among adults is estimated to be at least 10%. About 80% of these patients have preceding symptoms such as fever, diarrhea, or abdominal pain. Typically, these symptoms precede the arthritis by 1 week and are of short duration. The most commonly affected joints are the knees and ankles, but other joints can be involved. Typically, multiple (two to eight) joints become involved sequentially and asymmetrically over a period of a few days to 2 weeks, after which no additional joints are affected. Monoarticular arthritis occurs less commonly. In two-thirds of cases, the acute arthritis remits spontaneously within 1 to 3 months. Chronic joint disease is documented in a minority of cases. A few HLA-B27-positive patients with *Y. enterocolitica*-induced arthritis have subsequent ankylosing spondylitis, but this development is best explained by the fact that HLA-B27 is a major risk factor for each of these diseases. Mild, self-limited myocarditis accompanies about 10% of cases of *Yersinia*-induced arthritis

and can occur independently. Typical manifestations include cardiac murmurs and transient electrocardiographic abnormalities, such as prolongation of the PR interval and nonspecific ST-segment and T-wave changes. The syndrome of *Yersinia*-induced arthritis and carditis can be confused with acute rheumatic fever. In Scandinavia, erythema nodosum occurs in 15 to 20% of patients with yersiniosis, usually within a few days to 3 weeks after the onset of intestinal illness. Lesions typically are located on the lower extremities and resolve within 1 month. Less commonly reported nonsuppurative sequelae of *Y. enterocolitica* infections include reactive uveitis, iritis, conjunctivitis, urethritis, and glomerulonephritis. The complete triad of Reiter's syndrome (arthritis, conjunctivitis, and urethritis) is seen in 5 to 10% of patients with *Yersinia*-induced arthritis.

The most common clinical presentation of *Y. pseudotuberculosis* infection is fever and abdominal pain caused by mesenteric adenitis; diarrheal illness is less common than in *Y. enterocolitica* infection. Systemic manifestations, including septicemia, focal infections, reactive arthritis, and erythema nodosum, are generally similar to those associated with *Y. enterocolitica* infection. In addition, *Y. pseudotuberculosis* has been associated with a scarlet fever-like syndrome, acute interstitial nephritis, and hemolytic-uremic syndrome.

## LABORATORY FINDINGS AND DIAGNOSIS

Results of routine laboratory tests in most patients with yersiniosis are nonspecific. Leukocyte counts are usually normal or slightly elevated, often with a modest left shift. Standard microbiologic methods are sufficient to isolate *Y. enterocolitica* and *Y. pseudotuberculosis* from otherwise-sterile sites, such as blood,CSF, lymph node tissue, and peritoneal fluid, and from abscesses. Isolation of these organisms from feces is impeded by their slow growth and the overgrowth of normal fecal flora on culture media routinely used to select for enteric bacteria. When routine enteric media are used, the yield of yersinial isolates from feces is increased by incubation at 22 to 25°C for 48 h. The yield from feces and other grossly contaminated specimens can be further increased by the use of *Yersinia*-selective cefsulodin-Irgasan-novobiocin (CIN) agar and by cold enrichment (i.e., inoculation of feces into buffered saline and incubation at 4°C for 2 to 4 weeks, with periodic plating onto enteric media). Because bacteriologic procedures designed to isolate yersiniae from feces are not considered cost-effective, many laboratories undertake them by special request only.

The results of serologic tests can be used to support a diagnosis of yersiniosis. Agglutination tests orELISAsare used most commonly; immunoblotting has also been used. The existence of multiple serotypes makes routine serologic tests laborious; thus these tests are generally conducted only in research laboratories or large commercial laboratories. Since these tests are experimental and are neither standardized nor well validated, and since some strains of *Yersinia* cross-react with other bacteria (e.g., *Brucella*, *Salmonella*, and *Vibrio*) and with serum from some patients with thyroiditis, results should be interpreted with caution. In typical uncomplicated cases of yersiniosis, agglutinin titers begin to rise within the first week of illness, peak in the second week, and then gradually diminish and return to normal within 3 to 6 months, although agglutinating antibody may remain detectable for several years in some cases. Because an initial serum specimen is often collected a week or more after the onset of illness,

when agglutinin titers are already high, it is usually impossible to document a fourfold or greater rise in titer between paired specimens (although a fourfold or greater fall in titer may be found). Immunohistologic techniques and polymerase chain reaction tests to detect yersinial antigens and DNA, respectively, in clinical specimens are experimental at this time.

In patients with *Yersinia*-induced reactive arthritis, synovial fluid is sterile and the leukocyte count ranges from a few hundred to 60,000/uL, with a majority ofPMNs. The erythrocyte sedimentation rate is often >100 mm/h. Rheumatoid factor and antinuclear antibodies are usually absent. The diagnosis of *Yersinia*-induced reactive arthritis or other nonsuppurative inflammatory sequelae can be difficult, especially when triggering infections are asymptomatic or clinically mild or occur several weeks before the diagnosis is attempted. Because the isolation of a pathogenic *Yersinia* strain from feces is the most specific diagnostic test in such cases, it should be attempted. Since culture is of limited sensitivity in this clinical setting, a high index of suspicion and positive results of serologic tests for *Y. enterocolitica* or *Y. pseudotuberculosis* are usually required for diagnosis.

## TREATMENT

The effectiveness of antimicrobial agents in the treatment of yersinial enteritis, enterocolitis, mesenteric adenitis, or terminal ileitis has not been established. These conditions are usually self-limited, and their treatment is symptom-based and supportive. In uncomplicated cases, diarrhea should be treated with fluid and electrolyte replacement, with the route of delivery dependent on clinical severity. Enteric precautions are advisable for patients hospitalized with yersinial diarrhea. In general, antimicrobial treatment should be reserved for patients with septicemia, metastatic focal infections, or immunosuppression and enterocolitis. Controlled clinical comparisons of antimicrobial agents in the treatment of severe cases of yersiniosis have not yet been conducted. In such cases, drug selection should ultimately be guided by clinical response and bacterial sensitivity patterns. Clinical isolates of *Y. enterocolitica* and *Y. pseudotuberculosis* are usually susceptible in vitro to aminoglycosides, third-generation cephalosporins, chloramphenicol, quinolones, tetracyclines, and trimethoprim-sulfamethoxazole. In laboratory animals infected with enteropathogenic yersiniae, the fluoroquinolones have exerted the strongest bactericidal effects in vivo; clinical experience with these drugs against these pathogens in humans is promising but limited. Because they produceb-lactamases, isolates typically are resistant to penicillin, ampicillin, carbenicillin, and first-generation and most second-generation cephalosporins. Optimal dosages and durations of therapy have not been established. Mortality from *Y. enterocolitica* septicemia currently is ~10% despite treatment. Focal extraintestinal infections may require at least 3 weeks of therapy. No role for antimicrobial agents in the management of the nonsuppurative inflammatory manifestations of yersiniosis has been established. Patients with reactive arthritis may benefit from treatment with nonsteroidal anti-inflammatory drugs, intraarticular steroid injections, and physical therapy.

## PREVENTION AND CONTROL

The importance of safe food-handling and food-preparation practices in the prevention

of yersiniosis cannot be overemphasized. Caution is particularly warranted in the case of pork and other animal products. The consumption of raw or undercooked meats, especially pork, should be avoided. Increased efforts to prevent the spread of enteric pathogens in household, pet-care, day-care, and hospital settings and in the food industry would be likely to decrease the incidence of yersiniosis. Current regulations of the U.S. Food and Drug Administration require visual inspection of packed red cell units before transfusion, with the discarding of units in which bacterial contamination is suspected on the basis of darkening (reflecting decreased oxygen saturation and hemolysis). Since the risk is minimal, more specific measures to further decrease the likelihood of transfusion of *Y. enterocolitica*-contaminated blood products (e.g., limiting the period for which red cells can be stored before transfusion) are not considered cost-effective.

Yersiniosis is not routinely reportable to public health authorities in most jurisdictions. However, clinicians who suspect a common-source outbreak (e.g., because they have documented a familial case cluster or have diagnosed the disease in several apparently unrelated patients over a short period) or some other public health threat (e.g., because they have found occult *Y. enterocolitica* bacteremia in a recent blood donor) should consult promptly with local public health officials.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 163. *BARTONELLA* INFECTIONS, INCLUDING CAT-SCRATCH DISEASE - *Lucy Stuart Tompkins*

*Bartonella* spp., including *B. bacilliformis*, *B. henselae*, *B. quintana*, and *B. clarridgeiae*, are tiny gram-negative bacilli that can adhere to and invade mammalian cells, including endothelial cells and erythrocytes. Previously classified as *Rochalimaea* spp. within the rickettsia group, *Bartonella* spp. have now been removed from the order Rickettsiales on the grounds that they are not obligate intracellular parasites. These agents cause a wide spectrum of clinical illnesses, including trench fever, cat-scratch disease (CSD), bacillary angiomatosis, endocarditis, Oroya fever, and verruga peruana (Fig. 163-CD1). The pathologic manifestations of *Bartonella* disease vary with the immune status of the host.

### OROYA FEVER AND VERRUGA PERUANA

#### DEFINITION AND ETIOLOGY

Oroya fever and verruga peruana are caused by *B. bacilliformis*. Oroya fever is characterized by fever, profound anemia, and -- unless antibiotic treatment is given -- high mortality. The lesions referred to as verruga peruana may develop during the convalescent phase of Oroya fever or during chronic infection with *B. bacilliformis*. In 1885 Daniel Carrion, a Peruvian medical student, inoculated himself with blood from a patient with verruga peruana and subsequently died of Oroya fever, thus proving that both diseases are caused by a single agent.

#### EPIDEMIOLOGY

Infection with *B. bacilliformis* follows the bite of the sandfly vector *Phlebotomus*, an insect found in the river valleys of the Andes Mountains at altitudes of 600 to 2500 m. Oroya fever develops in nonimmune individuals who are not residents of the endemic region, whereas verruga peruana occurs in persons who apparently have been exposed in the past, including those who have recently had Oroya fever. The infection has not been acquired in the United States.

#### PATHOLOGY

During initial infection in the nonimmune host, *B. bacilliformis* cells adhere to erythrocytes and produce indentations in the cell membrane; the bacteria subsequently enter the erythrocytes and cause persistent deformation of the cytoskeleton. The parasitized erythrocytes are ultimately phagocytosed and destroyed. Although the life span of infected erythrocytes is markedly shortened, not all of this change can be attributed to the mechanical fragility induced by the internalization of bacteria. Decreased bone marrow erythropoiesis also contributes to anemia.

#### CLINICAL MANIFESTATIONS

The onset of symptoms in Oroya fever may be either insidious or abrupt, after an incubation period of approximately 3 weeks. The subacute presentation may include low-grade fever, malaise, headache, and anorexia. Sudden-onset disease commences

with high fever, chills, diaphoresis, headaches, and changes in mental status. These manifestations are followed by the sudden development of profound anemia, which is due to a marked decrease in erythrocyte numbers and is associated with macrocytic changes, poikilocytosis, Howell-Jolly bodies, nucleated erythrocytes, and immature myeloid cells. The leukocyte differential usually shifts to the left, although the total leukocyte count may be normal. The erythrocyte count may fall to extremely low levels. In eosin/thiazine-stained peripheral-blood smears, numerous microorganisms can be seen adhering to most erythrocytes.

During the acute phase, muscle and joint pain and headache may be severe; central nervous system changes include insomnia, delirium, and a decreased level of consciousness. Thrombocytopenic purpura may develop. If the patient survives, a convalescent phase ensues, characterized by the sudden disappearance of bacteria from blood smears, declining fever, and an increase in the erythrocyte count. Although much of the mortality associated with Oroya fever is due to profound anemia and toxicity, secondary bacterial infections (including salmonellosis and other enteric infections, malaria, and tuberculosis) are often an important contributing factor.

After convalescence from acute Oroya fever, verrugas may develop. These red or purple cutaneous lesions may be either tiny and sessile or large, pedunculated, and nodular. They bear a marked resemblance to the lesions of bacillary angiomatosis and to Kaposi's sarcoma.

### DIAGNOSIS

During acute infection, bacteria can be cultured from the blood on agar containing rabbit blood, with incubation at 28°C. The hallmark of verruga peruana is the formation of new blood vessels (angiogenesis) at the sites of bacterial replication.

### TREATMENT

Oroya fever responds to a variety of antimicrobial agents, including chloramphenicol, tetracyclines, penicillin, and streptomycin. Chloramphenicol is used most often because of its efficacy against most *Salmonella* infections (as salmonellosis may develop intercurrently). Verruga peruana may respond similarly; however, failure to respond to therapy and relapse are common and require the reinstitution of prolonged therapy.

## BACILLARY ANGIOMATOSIS

### DEFINITION AND ETIOLOGY

Bacillary angiomatosis was initially described as a condition occurring primarily in patients with AIDS and characterized by vascular cutaneous lesions resembling Kaposi's sarcoma. The disease can disseminate to involve virtually any organ system. Immunocompromised individuals, especially those infected with HIV, are at particularly high risk for bacillary angiomatosis, although in rare instances the patient is not obviously immunosuppressed. Both *B. henselae* and *B. quintana* (the infectious agent initially associated with trench fever) produce bacillary angiomatosis in persons with immunodeficiency.

## EPIDEMIOLOGY

Acquisition of *B. henselae* has been significantly associated with exposure to young cats infested with fleas (*Ctenocephalides felis)*. Because a high percentage of cats are seropositive, it has been suggested that patients with HIV infection avoid exposure to these animals. The finding that a large proportion of cats with fleas have persistent asymptomatic *B. henselae* bacteremia suggests that the domestic cat is the animal reservoir of this microorganism. The flea may serve as a transmitting vector in the cross-infection of cats, but its role in human infection is not clear. Tick-associated cases of *B. henselae* bacteremia have been reported in healthy immunocompetent individuals.

Person-to-person transmission of *B. quintana* by the human body louse (*Pediculus humanis corporis*) was documented during World War I under conditions of poor personal hygiene and sanitation. Although lice are suspected of transmission, the reservoir of *B. quintana* has not been identified.

A case-control study revealed that *B. henselae* and *B. quintana* differ significantly in terms of epidemiologic risk factors. All cases of *B. henselae* infection were associated with exposure to cats and their fleas and occurred sporadically, whereas the cases of *B. quintana* infection occurred in clusters and were associated with low socioeconomic status, homelessness, and exposure to body lice. Direct transmission of *B. henselae* from cats to their owners, presumably through cutaneous trauma, was supported by the matching DNA fingerprint patterns of isolates from the two sources.

## MICROBIOLOGY

*B. henselae* can be demonstrated in tissue by Warthin-Starry staining. Clumps and clusters of pleomorphic bacilli appear as purple deposits in tissue stained with hematoxylin and eosin. Although the bacteria may be difficult to cultivate in the laboratory, they can eventually be isolated from cultures of blood and of material from other sites. Colonies develop after prolonged incubation (1 to 4 weeks) on blood-containing media and pit the agar; bacterial cells are gram-negative. *B. quintana* grows as a smooth, nonpitting colony on solid agar after prolonged incubation.

Classification of *B. henselae* was first accomplished when molecular techniques were used to analyze bacterial ribosomal genes extracted from tissue samples. Definitive identification of *Bartonella* spp. is based on sequence analysis of 16S ribosomal DNA.

## PATHOGENESIS AND PATHOLOGY

Bacillary angiomatosis is characterized by a lobular proliferation of new blood vessels (angiogenesis) and a neutrophilic inflammatory response to myriad bacilli located within collagen-rich microscopic and macroscopic nodules. The endothelial cells lining the vascular spaces have a typical epithelioid appearance, and the lesions may resemble Kaposi's sarcoma histopathologically, although the characteristic spindle cell of the latter disease is usually absent. The bacterial and eukaryotic host factors that elicit the pathologic response are unknown.

## CLINICAL MANIFESTATIONS

The skin lesions of bacillary angiomatosis (also called *epithelioid angiomatosis*) are vascular nodules, papules, or tumors (Fig. 163-CD2) that range from tiny lesions resembling cherry angiomas or pyogenic granulomas to large, pedunculated, exophytic masses (Fig. 163-1). Characteristically, the lesions are red or purple, resembling Kaposi's sarcoma; they may be surrounded by an epithelial collarette, may be located anywhere on the skin, and may involve mucous membranes. The overlying epidermis may be focally ulcerated, and the underlying bone may be invaded and destroyed.

Dissemination of *B. henselae* infection occurs primarily in patients with cellular immune defects. Clinical manifestations accompanying dissemination are often nonspecific and include persistent fever, abdominal pain, weight loss, and malaise. Although the liver, spleen, bone marrow, and lymph nodes are primarily affected, HIV-infected patients may also develop central nervous system abnormalities (including psychiatric disorders and brain lesions), which are responsive to antibiotic therapy. Skin lesions usually are not evident in disseminated infection. Involvement of the liver or spleen may produce bacillary peliosis hepatis. Patients with the latter condition may report localized pain on palpation of the abdomen. Nodular lesions of variable size can be demonstrated by computed tomography or magnetic resonance imaging, with or without contrast agents.

In a case-control study of bacillary angiomatosis (see "Epidemiology" above), only *B. henselae* was associated with hepatosplenic disease (peliosis hepatis) and displayed a predilection for the lymph nodes. *B. quintana*, in contrast, was associated with osseous and subcutaneous infection.

## DIAGNOSIS

The diagnosis of bacillary angiomatosis is based primarily on the typical histopathologic findings of angiomas in association with clumps of tiny bacilli revealed by Warthin-Starry silver stain. Infection due to *B. henselae* can also be established by culture or by identification of specific DNA sequences. *B. henselae* is most easily isolated from blood through a lysis-centrifugation system. Colonies may be detected on blood-containing agar (rabbit blood is preferred) incubated with 5 to 10% $CO_2$ at 37°C for 2 to 4 weeks. *B. quintana* may be isolated from BACTEC (Becton Dickinson, Sparks, MD) aerobic bottles containing resin. Isolation from skin lesions and other tissues is more difficult but should be attempted when feasible. Initial reports suggested that cocultivation with endothelial cell monolayers was necessary; however, isolation by direct plating onto freshly prepared agar media has also been successful. Bacilli picked from new colonies but not subcultured may not stain, even with acridine orange; they stain weakly with safranin. Identification of *B. henselae* and *B. quintana* is based primarily on cellular fatty-acid analysis and polymerase chain reaction (PCR)-based restriction fragment length polymorphism analysis. Definitive identification of *Bartonella* spp. depends on DNA sequence analysis of 16S ribosomal RNA genes. The diagnosis ofCSD (see next section) can be made by specific serologic testing that detects *B. henselae*-specific antibodies, but the sensitivity and specificity of this method in patients with cutaneous and disseminated bacillary angiomatosis have not been determined.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cutaneous bacillary angiomatosis includes Kaposi's sarcoma, angiomas, and pyogenic granulomas. These conditions can be distinguished by histopathologic examination of biopsied material.

Cutaneous bacillary angiomatosis caused by *B. henselae* or *B. quintana* resembles verruga peruana, which is not seen outside of South America. In patients with AIDS, Kaposi's sarcoma lesions and bacillary angiomatosis may coexist.

### TREATMENT

Cutaneous lesions have been treated with a wide variety of antimicrobial drugs, including macrolides, tetracyclines, and antituberculous agents; *B. henselae* is susceptible to most antibiotics in vitro. Erythromycin (2 g/d), given orally for 3 weeks, is usually effective, as are newer macrolides; however, relapse may require prolonged therapy (3 weeks to 2 months) with an antibiotic that reaches an intracellular compartment, such as a macrolide or doxycycline (200 mg/d). Patients with peliosis hepatis should be treated with intravenous antibiotics, and those with disseminated disease or bacteremia should be treated with a prolonged course (3 weeks to 2 months) of systemic antibiotic, such as a macrolide (e.g., erythromycin, 2 g/d). In a case-control study of bacillary angiomatosis, treatment with a macrolide was associated with a therapeutic response and sterile tissue samples and may have been protective, whereas treatment with trimethoprim-sulfamethoxazole, ciprofloxacin, penicillins, or cephalosporins had no protective effect. Cutaneous lesions may or may not regress spontaneously, perhaps depending on the status of the host's immunity. The safety of ciprofloxacin in pregnant or lactating women has not been established. No antimicrobial has been studied prospectively, and information on efficacy comes only from case reports.

## CAT-SCRATCH DISEASE

### DEFINITION AND ETIOLOGY

TypicalCSD is manifested by painful regional lymphadenopathy persisting for several weeks or months after a cat scratch. Occasionally, infection may disseminate and produce more generalized lymphadenopathy and systemic manifestations, which may be confused with the manifestations of lymphoma. *B. henselae* is the causative agent of CSD. There is no evidence that *B. quintana* causes CSD, and this microbe is not carried by cats. The role of *Afipia felis* (originally proposed as the agent of CSD) is unclear inasmuch as only a few cases are associated with its isolation. *B. henselae* remains the predominant species causing typical CSD. Several reports suggest that *B. clarridgeiae* may also cause feline lymphadenopathy.

### EPIDEMIOLOGY

Approximately 60% of cases ofCSD in the United States occur in children. Exposure to bacteremic young cats that either are flea-infested or have been in contact with another cat carrying fleas poses a significant risk of infection. Most infections are caused by a scratch and only rare cases by a bite or by licking. Most cases occur in the warmer

months, when fleas are active. Regions of the United States where fleas are endemic have higher rates of infection. The flea may serve to transmit infection between cats; it is not known whether humans can be infected through the bite of an infected flea.

## CLINICAL MANIFESTATIONS

A localized papule, progressing to a pustule that often crusts over, develops 3 to 5 days after a cat scratch (Fig. 163-CD3). Tender regional lymphadenopathy develops within 1 to 2 weeks after inoculation; by this time, the papule may have healed spontaneously. Scratches are most often sustained on the hands or face, producing epitrochlear, axillary, pectoral, and cervical lymph node involvement. The involved nodes occasionally become suppurative; bacterial superinfection with staphylococci or other cutaneous pathogens may develop. Although most patients do not have fever, systemic symptoms are frequent and include malaise, anorexia, and weight loss. Without treatment, lymphadenopathy persists for weeks or even months and may be confused with lymphatic malignancy. Other manifestations in apparently immunocompetent patients include encephalitis, seizures and coma (especially in children), meningitis, transverse myelitis, granulomatous hepatitis and splenitis, osteomyelitis, and disseminated infection. Conjunctival inoculation may cause Parinaud's oculoglandular syndrome, with conjunctivitis and preauricular lymphadenopathy.

## PATHOLOGY

The histopathologic hallmark ofCSD is granulomatous inflammation with stellate necrosis but no evidence of angiogenesis. Thus, infection by *B. henselae* can produce two entirely different pathologic reactions, depending on the immune status of the host: CSD or bacillary angiomatosis.

## DIAGNOSIS

CSDshould be suspected if the patient has a history of exposure to cats and develops lymphadenopathy and a skin lesion. The diagnosis can be confirmed by pathologic examination of the involved nodes. Tiny bacilli in clusters can sometimes be seen in biopsy samples stained with Warthin-Starry silver. The CSD skin test, in which lymph node material obtained from patients with CSD serves as an antigen, is no longer used for diagnosis because of concerns about the transmission of viral agents. A specific serologic test has been developed and may produce a positive result in 70 to 90% of patients with intact immunity. The identification of *B. henselae* 16S ribosomal RNA genes in biopsy material by PCR amplification with specific oligonucleotide primers can also be diagnostically useful; however, these methods are not yet commercially available. Cultures of lymph nodes, cerebrospinal fluid, or other tissues are rarely positive.

## TREATMENT

AlthoughCSD is generally self-limited, tender regional lymphadenopathy and systemic symptoms may be debilitating. Patients with encephalitis or other serious manifestations should be treated with antibiotics. A randomized, double-blind, placebo-controlled trial demonstrated significant clinical benefit of treatment with oral azithromycin for 5 days in

cases of typical CSD (regimen for adults weighing >100 lb: one dose of 500 mg on day 1, 250 mg on days 2 through 5). Several reports suggest that aminoglycoside treatment (e.g., intravenous gentamicin at standard doses calculated to result in therapeutic levels) is effective in patients with encephalitis and other systemic infections. The oral agents that appear to be useful are those that also are most effective for the treatment of bacillary angiomatosis; they include ciprofloxacin, doxycycline, and azithromycin. Unlike bacillary angiomatosis, CSD responds to treatment with ciprofloxacin. The necessary duration of therapy is variable.

## TRENCH FEVER

### DEFINITION AND ETIOLOGY

Trench fever was first described as a debilitating febrile illness associated with prolonged *B. quintana* bacteremia in soldiers fighting in Europe during World War I. Although not usually fatal, the illness accounted for substantial morbidity. In recent years, trench fever has reemerged in the United States and has been caused by either *B. henselae* -- the agent ofCSD and bacillary angiomatosis -- or *B. quintana*.

### EPIDEMIOLOGY

Although trench fever was thought to have disappeared from the United States, recent cases have been diagnosed in homeless persons (*B. quintana*) and in persons bitten by ticks (*B. henselae*). During World War I, trench fever was transmitted from person to person by the human body louse. Transmission by ectoparasites is suspected in the recent cases of *B. quintana* infection but has not been firmly documented. Patients with trench fever have apparently normal immune defenses.

### CLINICAL MANIFESTATIONS

Trench fever is characterized by the sudden onset of headache, aseptic meningitis, persistent fever (which can be high-grade and is commonly paroxysmal), malaise, weight loss, and other nonspecific symptoms. Severe musculoskeletal pain is more common among immunocompetent than among immunocompromised patients. Bacteremia can persist for days or weeks, and relapses have followed short courses of antibiotic therapy. Localized findings are uncommon.

### DIAGNOSIS

Trench fever is diagnosed by the finding of sustained bacteremia. *B. henselae* and *B. quintana* grow slowly. Colonies develop on rabbit blood agar after 1 to 4 weeks of incubation under conditions of increased $CO_2$. Serologic tests for this disease have not yet been standardized.

### TREATMENT

A prolonged course (4 weeks) of antimicrobial therapy may be required. Agents that can cross the mammalian cell membrane are most effective, including erythromycin (2 g/d) or azithromycin (500 mg/d). Data on the efficacy of these agents come from a limited

number of case reports.

## OTHER *BARTONELLA* INFECTIONS, INCLUDING CULTURE-NEGATIVE ENDOCARDITIS

The application of molecular methods to the detection of microorganisms that are difficult to cultivate in the laboratory has revealed new *Bartonella* spp. and has established *Bartonella* spp. as a cause of endocarditis cases previously classified as being of unknown etiology. *B. quintana* is the most frequently isolated *Bartonella* species in these cases. Two new species, *B. elizabethae* and *B. clarridgeiae*, as well as *B. henselae* have also been identified as agents of subacute and chronic endocarditis.

The diagnosis of *Bartonella* endocarditis is confirmed by blood cultures. Specific antibodies are produced; however, *B. quintana* infection may produce antibodies that cross-react with *Chlamydia pneumoniae*.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 164. DONOVANOSIS - *Gavin Hart*

Donovanosis is a chronic, progressively destructive bacterial infection of the genital region that is generally regarded as sexually transmitted. The disease has been known by many other names, the most common of which are granuloma inguinale and granuloma venereum.

### ETIOLOGY

Donovanosis is caused by *Calymmatobacterium granulomatis*, an intracellular, gram-negative, pleomorphic, encapsulated (when mature) bacterium measuring 1.5 by 0.7 um. *C. granulomatis* shares many morphologic and serologic characteristics and >99% homology at the nucleotide level with *Klebsiella* species that are pathogenic to humans. Polymerase chain reaction amplification of the *phoE* gene shows it to be closely related to that in *Klebsiella pneumoniae*, *K. rhinoscleromatis*, and *K. ozaenae*. Electron microscopy shows typical gram-negative morphology and a large capsule but no flagella. Filiform or vesicular protrusions occur on a corrugated cell wall.

### EPIDEMIOLOGY

Donovanosis is endemic among Aborigines in central Australia as well as in Papua New Guinea, southeastern India, southern Africa, and the Caribbean and adjacent areas of South America. In the first half of the twentieth century, the disease was endemic in parts of the United States (with an estimated 5000 to 10,000 cases in 1947); small epidemics still occur in this country and in other developed countries. Over 70% of cases involve persons 20 to 40 years of age. The infection is predominantly sexually transmitted, but extragenital skin lesions can follow transmission from concurrent genital lesions via the fingers or through other nonsexual contact, and autoinoculation may produce new lesions from contact with adjacent skin ("kissing" lesions). Infants born to infected mothers have acquired infection at birth.

The classification of donovanosis as a sexually transmitted disease (STD) has been disputed because of cases in young children and occasionally in sexually inactive individuals, transmission by direct body contact and via inanimate intermediaries, and the low and variable prevalence of donovanosis among sexual partners (0.4 to 52%). The dominance of sexual transmission is suggested by the combined factors of lesions predominantly affecting the genitalia, the highest prevalence among persons in age and socioeconomic groups that are most often affected by STDs, and the predictable occurrence of disease in visitors to areas of endemicity following sexual exposure.

### CLINICAL MANIFESTATIONS

The incubation period is usually 1 to 4 weeks but may extend to 1 year. Skin lesions have been detected in infants 6 weeks to 6 months after birth. The disease begins as one or more subcutaneous nodules that erode through the skin to produce clean, granulomatous, sharply defined, usually painless lesions (Fig. 164-1). These lesions, which bleed readily on contact, slowly enlarge. The genitalia are involved in 90% of cases, the inguinal region in 10%, and the anal region in 5 to 10%. Genital swelling, particularly of the labia, is a common feature and occasionally progresses to

pseudoelephantiasis. Phimosis and paraphimosis are common local complications, and progressive erosion of affected tissues may completely destroy the penis or other organs. Less common clinical variants include a hypertrophic form (cauliflower- or wartlike lesions), a necrotic form (destructive lesions with foul-smelling exudate, often resembling amebiasis), and a sclerotic or cicatricial form, which has a dry base with extensive scar tissue (Fig. 132-CD3).

Extragenital lesions occur in at least 6% of cases. Oral donovanosis, the most common extragenital manifestation, presents as pain or bleeding in the mouth, lesions on the lips, or extensive swelling of the gums and palate. Donovanosis may affect most bones, and sometimes many bones are affected at the same time; the tibia is involved in over 50% of such cases. Bony lesions are associated with constitutional symptoms (weight loss, fever, night sweats, and malaise) and are usually found in women. More than 50% of women have primary lesions on the cervix. Prompt pelvic examinations and early diagnosis are likely to substantially decrease the morbidity and mortality (a likely outcome in misdiagnosed spinal lesions) associated with extragenital donovanosis in women.

## DIAGNOSIS

**Laboratory Diagnosis** The preferred method involves demonstration of typical intracellular Donovan bodies within large mononuclear cells visualized in smears prepared from lesions or biopsy specimens. With typical beefy lesions, a small piece of tissue is removed with forceps and scalpel, and a crush impression of the deep surface is made on a glass slide. The smear is air-dried, heat-fixed, and stained with Giemsa, Leishman's, or Wright's stain. For dry, flat, or necrotic lesions, a punch-biopsy specimen should be obtained from the advancing edge. This specimen can be used to prepare a smear or embedded for histologic examination (with a silver stain). Histologic examination shows epithelial proliferation, often simulating neoplasia, with a heavy inflammatory infiltrate of plasma cells, some neutrophils, and few if any lymphocytes. The large mononuclear cells are 25 to 90 um in diameter, with a vesicular or pyknotic nucleus. Up to 20 intracytoplasmic vacuoles contain pleomorphic Donovan bodies in either young uncapsulated forms (which often resemble closed safety pins) or mature capsulated forms. *C. granulomatis* has never been grown on artificial solid media but has been cultured in chicken embryonic yolk sacs, on human monocytes, and on human epithelial (HEp-2) cells. A sensitive and specific serologic test, based on indirect immunofluorescence, has been developed.

**Differential Diagnosis** Condylomata lata of secondary syphilis may be confused with donovanosis; however, these lesions usually appear as white or pale moist plaques in the anogenital area, whereas the lesions of donovanosis are usually bright red. Syphilis and donovanosis frequently coexist because syphilis is usually highly prevalent in areas where donovanosis is endemic; thus positive syphilis serology does not exclude a diagnosis of donovanosis. Condylomata lata subside within 1 week of treatment with benzathine penicillin (2.4 million units), whereas donovanosis lesions remain unchanged.

The necrotic form of donovanosis may resemble squamous cell carcinoma; likewise, cervical and vulvar lesions may closely resemble carcinoma. Penile amebiasis may

resemble necrotic donovanosis but usually follows anal intercourse and is much less common than donovanosis in areas where the latter is endemic. Atypical clinical variants of chancroid, referred to as *pseudogranuloma inguinale*, have been described in patients seen at clinics in Atlanta. Disseminated donovanosis lesions of bones, particularly in the spine, can mimic tuberculosis. Lesions that produce draining sinuses near the jaw may simulate actinomycosis. The histologic findings of donovanosis must be distinguished from those of rhinoscleroma, leishmaniasis, and histoplasmosis. Genital ulcers are a risk factor for HIV acquisition in developing countries, and patients with donovanosis should be tested for HIV infection.

**TREATMENT**

Table 164-1 shows the most effective regimens for treating donovanosis. Doxycycline is the first choice for therapy in developed countries. Erythromycin provides an effective option for pregnant patients, and azithromycin is an effective alternative that is more convenient to administer. Extensive lesions have been cured with oral azithromycin at a dosage of 500 mg/d, but the more convenient dose of 1 g weekly is also effective. Although chloramphenicol is the drug of choice in some developing countries, it is unlikely to be acceptable in developed countries because of bone marrow toxicity. Penicillin is not effective for treating donovanosis. Patients should be examined weekly, and therapy should be continued until lesions have healed (3 to 5 weeks, except in severe cases). If antibiotic therapy is stopped earlier, lesions often continue to heal, but the relapse rate is higher. If the lesions are unchanged after 2 weeks of treatment, an alternative antibiotic regimen should be used.

The treatment regimens just described are usually adequate in HIV-infected patients without immunosuppression, but an increasing failure rate has been reported in immunosuppressed patients, for whom daily administration of azithromycin is recommended if other regimens fail to elicit a response.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 7 -MISCELLANEOUS BACTERIAL INFECTIONS

### 165. NOCARDIOSIS - *Gregory A. Filice*

The term *nocardiosis* refers to invasive disease associated with members of the genus *Nocardia*. Of the several distinctive syndromes, pneumonia and disseminated disease are most common. Others include cellulitis, lymphocutaneous syndrome, actinomycetoma, and keratitis.

#### MICROBIOLOGY

Nocardiae are saprophytic aerobic actinomycetes that are common worldwide in soil, where they contribute to decay of organic matter. Nocardial taxonomy is complex and incompletely understood. Seven species have been associated with human disease: *N. asteroides*, *N. brasiliensis*, *N. otitidis-caviarum* (formerly *N. caviae*), *N. farcinica*, *N. nova*, *N. transvalensis*, and *N. pseudobrasiliensis*. *N. asteroides* is the species most commonly associated with invasive disease. *N. farcinica* is less common but tends to be virulent and prone to dissemination. The new species *N. pseudobrasiliensis* accounts for most cases of invasive disease previously attributed to *N. brasiliensis*. True *N. brasiliensis* isolates are usually associated with disease limited to the skin. *N. transvalensis* is generally associated with mycetoma or, in immunosuppressed persons, with pulmonary or systemic disease.

#### EPIDEMIOLOGY

Approximately 1000 cases of nocardial infection are diagnosed annually in the United States, 85% of them pulmonary and/or systemic. The disease is more common among adults and males. Outbreaks, which are rare, have been associated with contamination of the hospital environment, solutions, or drug injection equipment. Person-to-person spread is not well documented. There is no known seasonality.

The risk of pulmonary or disseminated disease is greater than usual among people with deficient cell-mediated immunity, especially that associated with lymphoma, transplantation, or AIDS. In persons with AIDS, nocardiosis usually presents at a $CD4_+$lymphocyte concentration of <250/uL. Prophylaxis with sulfamethoxazole and trimethoprim appears to reduce the risk of nocardiosis in persons with AIDS or transplanted organs. Nocardiosis has also been associated with pulmonary alveolar proteinosis, tuberculosis and other mycobacterial diseases, and chronic granulomatous disease.

*N. brasiliensis*, *N. asteroides*, *N. otitidis-caviarum*, and *N. transvalensis* are associated with actinomycetoma. Cases occur mainly in tropical and subtropical regions, especially those of Mexico, Central and South America, Africa, and India. The most important risk factor is frequent contact with soil or vegetable matter.

#### PATHOLOGY AND PATHOGENESIS

Pneumonia and disseminated disease are both thought to follow inhalation of fragmented bacterial mycelia. The characteristic histologic feature of nocardiosis is an

abscess with extensive infiltration by neutrophils and prominent necrosis. Granulation tissue usually surrounds the lesions, but extensive fibrosis or encapsulation is uncommon. Actinomycetoma is characterized by suppurative inflammation with sinus tract formation. Granules -- microcolonies composed of dense masses of bacterial filaments extending radially from a central core -- are occasionally observed in histologic preparations. They are frequently found in discharges from lesions of actinomycetoma but almost never from lesions in other forms of nocardiosis.

Nocardiae have evolved a number of properties that enable them to survive within phagocytes, including neutralization of oxidants, prevention of phagosome-lysosome fusion, and prevention of phagosome acidification. Neutrophils phagocytose the organisms and limit their growth but do not kill them efficiently. Cell-mediated immunity is important for definitive control and elimination of nocardiae.

## CLINICAL MANIFESTATIONS

**Respiratory Tract Disease** Pneumonia is by far the most common respiratory tract nocardial disease. Nocardial pneumonia is typically subacute; symptoms have usually been present for days or weeks at presentation. The onset may be more acute in immunosuppressed patients. Cough is prominent and produces small amounts of thick, purulent sputum that is not malodorous. Fever, anorexia, weight loss, and malaise are common; dyspnea, pleuritic pain, and hemoptysis are less common. Remissions and exacerbations over several weeks are frequent.

Roentgenographic patterns are variable (Fig. 165-CD1), but some characteristics are highly suggestive. Infiltrates vary in size and are typically of at least moderate density. Single or multiple nodules are common, sometimes suggesting metastatic tumors. Infiltrates and nodules tend to cavitate. Empyema is present in one-third of cases.

Nocardiosis may spread directly from the lungs to adjacent tissues. Pericarditis, mediastinitis, and the superior vena cava syndrome have all been reported. Spread through the chest wall is rare.

Nocardial laryngitis, tracheitis, and bronchitis are much less common than pneumonia. In the major airways, disease often presents as a nodular or granulomatous mass. A few cases of sinusitis have been reported.

Nocardiae are sometimes isolated from respiratory secretions of patients without apparent nocardial disease. Most of these patients have chronic pulmonary disease with abnormal airways or parenchyma.

**Extrapulmonary Dissemination** In half of all cases of pulmonary nocardiosis, disease appears outside the lungs. In one-fifth of cases of disseminated disease, lung disease is not apparent. The most common site of dissemination is the brain. Other common sites include the skin and supporting structures, kidneys, bone, and muscle, but almost any organ can be involved. Peritonitis and endocarditis have been reported. The typical manifestation of extrapulmonary dissemination is a subacute abscess. A minority of abscesses outside the lungs or central nervous system (CNS) form fistulae and discharge small amounts of pus. Nocardiae have been recovered from blood in a few

cases of pneumonia or disseminated disease.

InCNSinfections, brain abscesses are usually supratentorial, are often multiloculated, and may be single or multiple (Fig. 165-1, 165-CD2). Brain abscesses tend to burrow into the ventricles or extend out into the subarachnoid space. The symptoms and signs are somewhat more indolent than those of other types of bacterial brain abscess. Meningitis is uncommon and is usually due to spread from a nearby brain abscess. Nocardiae are not easily recovered from cerebrospinal fluid (CSF).

**Disease Following Transcutaneous Inoculation** Disease following transcutaneous nocardial inoculation usually takes one of three forms: cellulitis, lymphocutaneous syndrome, or actinomycetoma. Cellulitis generally begins 1 to 3 weeks after a recognized breach of the skin, often with soil contamination. Subacute cellulitis with pain, swelling, erythema, and warmth develops over days to weeks. The lesions are usually firm and nonfluctuant. Disease may progress to involve underlying muscle, tendon, bones, or joints. Dissemination is rare. *N. asteroides* is common in colder climates, while *N. brasiliensis* predominates in warmer climates.

In the lymphocutaneous syndrome, there is typically a pyodermatous lesion at the site of inoculation, with central ulceration and purulent or honey-colored drainage. Subcutaneous nodules often appear along lymphatics that drain the primary lesion. The lymphangitic form closely resembles lymphocutaneous sporotrichosis (Chap. 208). Most cases of the lymphocutaneous syndrome are associated with *N. brasiliensis*.

Actinomycetoma usually begins with a nodular swelling, sometimes at a site of local trauma. Lesions typically develop on the feet or hands but may involve the posterior part of the neck, the upper back, the head, and other sites. The nodule eventually breaks down and a fistula appears. This fistula is soon accompanied by others. The fistulas tend to come and go, with new ones forming as old ones disappear. The discharge is serous or purulent, may be bloody, and often contains 0.1- to 2-mm white granules consisting of masses of mycelia. The lesions spread slowly along fascial planes to involve adjacent areas of skin, subcutaneous tissue, and bone. Over months or years, there may be extensive deformation of the affected part. Lesions involving soft tissues are only mildly painful; those affecting bones or joints are more so. Systemic symptoms are absent or minimal. Infection rarely disseminates from actinomycetoma, and lesions on the hands and feet usually cause only local disability. Lesions on the head, neck, and trunk can invade locally to involve deep organs and result in severe disability or death.

**Keratitis** *Nocardia* spp., usually *N. asteroides*, are uncommon causes of subacute keratitis. The infection usually follows eye trauma. Nocardial infection of lacrimal glands has been reported. Disease involving deeper eye structures is usually a manifestation of dissemination.

## DIAGNOSIS

The first step in diagnosis is examination of sputum or pus for crooked, branching, beaded, gram-positive filaments 1 um wide and up to 50 um long. Most nocardiae are acid-fast in direct smears if a weak acid is used for decolorization (e.g., in the modified Kinyoun, Ziehl-Neelsen, and Fite-Faraco methods) (Fig. 165-CD3). The organisms often

take up silver stains. Nocardiae grow relatively slowly; colonies may take up to 2 weeks to appear and may not develop their characteristic appearance for up to 4 weeks. Several blood culture systems support nocardial growth. Yield is enhanced when blood cultures are incubated aerobically for up to 4 weeks and when blind subcultures are performed. Nocardial growth is so different from that of more common pathogens that the laboratory should be alerted when nocardiosis is suspected to maximize the likelihood of isolation. Since nocardiae are among the few aerobic microorganisms that use paraffin as a carbon source, paraffin baiting can be useful in isolating the organisms from mixed cultures.

In cases of pneumonia, sputum smears are often negative. Unless the diagnosis can be made in these cases by sampling lesions in other, more accessible sites, bronchoscopy or lung aspiration is usually necessary. Transtracheal aspiration should be avoided, as it frequently leads to nocardial cellulitis in tissues around the puncture wound.

In patients with nocardial pneumonia, a careful history should be obtained and a thorough physical examination performed to evaluate the possibility of dissemination. Suggestive symptoms or signs should be pursued with further diagnostic tests. Computed tomography or magnetic resonance imaging of the head, with and without contrast material, should be undertaken if signs or symptoms suggest brain involvement. Many authorities recommend brain imaging in all cases of pulmonary or disseminated disease.

When clinically indicated,CSF or urine should be concentrated and then cultured. In actinomycetoma cases, granules should be sought in the discharge. Suspect particles should be washed in saline, examined microscopically, and cultured.

Isolation of nocardiae from sputum or blood occasionally represents colonization, transient infection, or contamination. In typical cases of respiratory tract colonization, Gram-stained specimens are negative and cultures are only intermittently positive. A positive sputum culture in an immunosuppressed patient usually reflects disease. When nocardiae are isolated from an immunocompetent patient without apparent nocardial disease, the patient should be observed carefully without treatment. A patient with a host-defense defect that increases the risk of nocardiosis should usually receive antimicrobial treatment.

*Nocardia* spp. are difficult to differentiate from one another with standard biochemical tests, and isolates from patients with systemic or severe disease should be sent to a reference laboratory for definitive identification and antimicrobial susceptibility testing. Susceptibility results, which help differentiate species, are of less certain clinical value but sometimes guide therapy in difficult cases.

In vitro, strains of *N. farcinica* differ from most in that they are usually resistant to cephalosporins and in one-fifth of cases are resistant to imipenem. *N. pseudobrasiliensis* strains often exhibit resistance to minocycline or amoxicillin/clavulanic acid and susceptibility to ciprofloxacin or clarithromycin. *N. transvalensis* displays increased resistance to many antimicrobial agents, including amikacin, tobramycin, cefotaxime, ceftriaxone, and amoxicillin/clavulanic acid. *N. nova* isolates appear to be susceptible to ampicillin and erythromycin in vitro but also produce

b-lactamase constitutively or in the presence of ab-lactam.

Several presumptive diagnostic tests for nocardial infection have been studied, including tests for antibodies, nocardial metabolites, and nocardial DNA. None is ready for clinical use at this time.

## TREATMENT

Sulfonamides are the drugs of choice for nocardiosis (Table 165-1). Initially, 6 to 8 g of sulfadiazine or sulfisoxazole per day in four divided doses should be used. After disease is controlled, 4 g/d can be used to complete therapy. In difficult cases, sulfonamide levels should be measured and dosages adjusted to keep serum levels between 100 and 150 ug/mL. The combination of sulfamethoxazole (SMZ) and trimethoprim (TMP) is probably equivalent to sulfonamides; some authorities believe that the combination may in fact be more effective, but it also poses a modestly greater risk of hematologic toxicity. At the outset, 10 to 20 mg of TMP per kg and 50 to 100 mg of SMZ per kg should be given each day in two divided doses. Later, the daily doses can be decreased to as little as 5 mg/kg and 25 mg/kg, respectively. In persons with sulfonamide allergies, desensitization usually allows continuation of therapy with these effective and inexpensive drugs.

Minocycline is the best-established alternative oral drug and should be given in doses of 100 to 200 mg twice a day. Other tetracyclines are usually ineffective. *N. nova* infections can be treated with erythromycin (500 to 750 mg four times a day) and/or ampicillin (1 g four times a day), but other *Nocardia* spp. are often resistant to both drugs. Amoxicillin (500 mg) combined with clavulanic acid (125 mg), given three times a day, has been effective in a few cases but should be avoided in cases due to *N. nova*, in which clavulanate inducesb-lactamase production. Ofloxacin (400 mg twice a day) and clarithromycin (500 mg twice a day) have each been successful in a few cases.

Amikacin, the best-established parenteral drug, is given in doses of 5 to 7.5 mg/kg every 12 h. Serum levels should be monitored with prolonged therapy in patients with diminished renal function and in the elderly. Newer b-lactam antibiotics, including cefotaxime, ceftizoxime, ceftriaxone, and imipenem, are usually effective. They may be less effective in some cases caused by *N. farcinica*.

In patients receiving immunosuppressive therapy, the regimen should be continued if necessary for treatment of an underlying disease or prevention of transplant rejection. In many cases, two or more antimicrobial agents have been used to treat nocardiosis, often in combinations including a sulfonamide or minocycline. Whether such therapy is better than monotherapy is not known, and combination therapy increases the risk of toxicity.

Surgical management of nocardial disease is similar to that of other bacterial diseases. Brain abscesses should be aspirated, drained, or excised if the diagnosis is unclear, if an abscess is large and accessible, or if an abscess fails to respond to chemotherapy. Abscesses that are small or inaccessible should be treated medically; in these cases, clinical improvement should be noticeable within 1 to 2 weeks. Brain imaging should be repeated to document the resolution of lesions, although abatement on images often

lags behind clinical improvement.

Antimicrobial therapy usually suffices for nocardial actinomycetoma. In deep or extensive cases, drainage or excision of heavily involved tissue may facilitate healing, but structure and function should be preserved whenever possible.

Nocardial infections tend to relapse (particularly in patients with chronic granulomatous disease), and long courses of antimicrobial therapy are necessary. If disease is unusually extensive, if the patient is immunosuppressed, or if the response to therapy is slow, the recommendations in Table 165-1 should be exceeded.

The mortality rate for pulmonary or disseminated nocardiosis outside theCNSshould be <5%. CNS disease carries a higher mortality rate. Patients should be followed carefully for at least 6 months after therapy has ended. Any child with nocardiosis and no known cause of immunosuppression should undergo tests to determine the adequacy of the phagocytic respiratory burst.

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Back to Table of Contents

## 166. ACTINOMYCOSIS - *Thomas A. Russo*

Actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, primarily of the genus *Actinomyces*, that colonize the mouth, colon, and vagina. Mucosal disruption may lead to infection at virtually any site in the body. The clinical presentations of actinomycosis are myriad; however, classic features include purulent foci surrounded by dense fibrosis that, over time, cross natural anatomic boundaries into contiguous structures, with the formation of fistulae and sinus tracts in some cases. In vivo growth of actinomycetes usually results in the formation of clumps called *grains* or *sulfur granules*. This infection is commonly confused with a neoplasm. Common in the preantibiotic era, actinomycosis has diminished in incidence, as has its timely recognition. Actinomycosis has been called "the most misdiagnosed disease," and it has been said that "no disease is so often missed by experienced clinicians." Thus this entity remains a diagnostic challenge. An awareness of the full spectrum of the disease will expedite its diagnosis and treatment and will minimize the unnecessary surgical interventions, morbidity, and mortality that are reported all too often.

### ETIOLOGIC AGENTS

Actinomycosis is most commonly caused by *A. israelii*. *A. naeslundii*, *A. odontolyticus*, *A. viscosus*, *A. meyeri*, *A. gerencseriae*, and *Propionibacterium propionicum* are established but less common causes of the disease. Most if not all actinomycotic infections are polymicrobial. *Actinobacillus actinomycetemcomitans*, *Eikenella corrodens*, Enterobacteriaceae, and species of *Fusobacterium*, *Bacteroides*, *Capnocytophaga*, *Staphylococcus*, and *Streptococcus* are commonly isolated with actinomycetes in various combinations, depending on the site of infection. The contribution of these other species to the pathogenesis of actinomycosis is uncertain.

An increasing number of bacterial species isolated from human clinical specimens have recently been classified as *Actinomyces*. Although their role in disease has not always been defined, *A. europaeus*, *A. neuii* subspecies *neuii*, *A. neuii* subspecies *anitratus*, *A. radingae*, *A. graevenitzii*, and *A. turicensis* appear to be infrequent and often opportunistic human pathogens. The nature of the infections described to date does not clearly establish these agents as causes of the typical syndrome of actinomycosis.

### EPIDEMIOLOGY

The agents of actinomycosis are members of the normal oral flora and are often cultured from the bronchi, the gastrointestinal tract, and the female genital tract. Infection occurs throughout life, with a peak incidence in the middle decades. Males have a threefold higher incidence of infection, possibly because of poorer dental hygiene and/or more frequent trauma. Likely contributing factors to the decrease in the incidence of actinomycosis since the preantibiotic era include improved dental hygiene and the initiation of antimicrobial treatment early on -- before the full development of the disease. Individuals who do not seek or have access to health care are undoubtedly at higher risk.

### PATHOGENESIS AND PATHOLOGY

A vital step in the development of actinomycosis is disruption of the mucosal barrier, which allows the actinomycetes to invade beyond their endogenous habitat in the mouth, lower gastrointestinal tract, and female genitourinary tract. Local infection, subsequent extension, and (in rare instances) distant hematogenous seeding may ensue. Initial acute inflammation is followed by the characteristic chronic, indolent phase. Lesions usually appear as single or multiple indurations. Central fluctuance, with pus containing neutrophils and sulfur granules, is virtually diagnostic of this disease (Fig. 166-1). The fibrous walls of the mass are typically described as "woody." The responsible bacterial and/or host factors have not yet been identified. Once established, actinomycosis spreads contiguously in a slow progressive manner, ignoring tissue planes. Given time, sinus tracts, which can spontaneously close and reopen, will form and extend to skin, adjacent organs, or bone. These unique features of actinomycosis mimic malignancy, with which it is often confused.

Foreign bodies appear to facilitate infection. This association most frequently involves intrauterine contraceptive devices (IUCDs). In addition, an increasing number of reports have described an association of actinomycosis with HIV infection, transplantation, and chemotherapy. Ulcerative mucosal infections (e.g., by herpes simplex virus or cytomegalovirus) and abnormalities in host defenses may facilitate the development of actinomycosis in the latter settings.

## CLINICAL MANIFESTATIONS

**Oral-Cervicofacial Disease** Actinomycosis occurs most frequently at an oral, cervical, or facial site, usually as a soft tissue swelling, abscess, or mass lesion that is often mistaken for a neoplasm. The angle of the jaw is generally involved, but a diagnosis of actinomycosis should be considered with any mass lesion or relapsing infection in the head and neck. Otitis, sinusitis, and canaliculitis can also develop. Pain, fever, and leukocytosis are variably reported. Contiguous extension to the cranium, cervical spine, or thorax is a potential sequela.

**Thoracic Disease** Thoracic actinomycosis usually follows an indolent progressive course, with involvement of the pulmonary parenchyma and/or the pleural space. Chest pain, fever, and weight loss are common. A cough, when present, is variably productive. The usual radiographic appearance is either a mass lesion or pneumonitis. Cavitary disease or hilar adenopathy may develop. More than 50% of cases include pleural thickening, effusion, or empyema. Rarely, pulmonary nodules or endobronchial lesions occur. Pulmonary lesions suggestive of actinomycosis may cross fissures or pleura; may involve the mediastinum, contiguous bone, or chest wall; or may be associated with a sinus tract. In the absence of these findings, thoracic actinomycosis is usually mistaken for a neoplasm or for pneumonitis due to more usual causes.

Mediastinal infection is uncommon, usually arising from thoracic extension but rarely resulting from perforation of the esophagus, from trauma, or from head and neck or abdominal disease. The structures within the mediastinum and the heart can be involved in various combinations; consequently, the possible presentations are diverse. Isolated disease of the breast has been described.

**Abdominal Disease** Abdominal actinomycosis poses a great diagnostic challenge. Months or years usually pass from the inciting event (e.g., appendicitis, diverticulitis, peptic ulcer disease, foreign-body perforation, bowel surgery, or ascension fromIUCD-associated pelvic disease) to clinical recognition. Because of the flow of peritoneal fluid and/or the direct extension of primary disease, virtually any abdominal organ, region, or space can be involved. The disease usually presents as an abscess or a mass lesion that is often fixed to underlying tissue and mistaken for a tumor. Infiltrative disease with irregular contrast enhancement may be seen on computed tomography (CT). Sinus tracts to the abdominal wall or perianal region may develop. Recurrent disease or a wound or fistula that fails to heal (in the absence of inflammatory bowel disease) suggests actinomycosis.

Hepatic infection usually presents as single or multiple abscesses or masses. Isolated disease presumably develops via hematogenous seeding from cryptic foci. Presently available imaging and percutaneous techniques have resulted in improved diagnosis and treatment.

All levels of the urogenital tract can be infected. Renal disease usually presents as pyelonephritis and/or renal and perinephric abscess. Bladder involvement, usually due to extension of pelvic disease, may result in ureteral obstruction or fistulas to bowel, skin, or uterus.

**Pelvic Disease** Actinomycotic involvement of the pelvis occurs most commonly in association with anIUCD. Pelvic symptoms when an IUCD is in place or has recently been removed should prompt consideration of actinomycosis. Although the risk has not yet been quantified, it appears to be small. The disease rarely develops when the IUCD has been in place for <1 year, but the risk increases with time. Actinomycosis can also present months after the removal of the device. Symptoms are typically indolent; fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge are the most common. The earliest stage of disease -- often endometritis -- commonly progresses to pelvic masses or a tuboovarian abscess (Fig. 166-2). Unfortunately, because the diagnosis is often delayed, a "frozen pelvis" mimicking malignancy or endometriosis can develop by the time of recognition.

An unresolved issue is whether the isolation of *Actinomyces*-like organisms (ALOs) from cultures of cervical or endometrial specimens or the detection of ALOs by immunofluorescence is correlated withIUCD-associated disease. A Papanicolaou smear may fail to detect ALOs even in the presence of active actinomycosis. Although the risk appears to be small, the consequences of infection are significant. Therefore, until more quantitative data become available, detection of ALOs or immunofluorescence-positive organisms in conjunction with symptoms that cannot be accounted for appears to warrant removal of the IUCD and -- if advanced disease is excluded -- initiation of a 14-day course of empirical treatment for possible early pelvic actinomycosis. The detection of ALOs or immunofluorescence-positive organisms in the absence of symptoms warrants education of the patient and close follow-up but not removal of the IUCD.

**Central Nervous System Disease** Actinomycosis of the central nervous system is rare. Single or multiple brain abscesses are most common. An abscess usually appears

onCT as a ring-enhancing lesion with a thick wall that may be irregular or nodular. Meningitis, epidural or subdural space infection, and cavernous sinus syndrome have also been described.

**Musculoskeletal Infection** Actinomycotic infection of the bone is usually due to adjacent soft tissue infection but may be associated with trauma (e.g., fracture of the mandible) or hematogenous spread. Because of slow disease progression, new bone formation and bone destruction are seen concomitantly. Infection of an extremity is uncommon and is usually a result of trauma. Skin, subcutaneous tissue, muscle, and bone (with periostitis or acute or chronic osteomyelitis) are involved alone or in various combinations. Cutaneous sinus tracts frequently develop.

**Disseminated Disease** Hematogenous dissemination of disease from any location rarely results in multiple organ involvement. The lungs and liver are most commonly affected, with the presentation of multiple nodules mimicking disseminated malignancy. The clinical presentation may be surprisingly indolent given the extent of disease.

## DIAGNOSIS

The diagnosis of actinomycosis, particularly when it mimics malignancy, is rarely considered. All too often, the first mention of actinomycosis is by the pathologist after extensive surgery has been performed. Since medical therapy alone is often sufficient for cure, the challenge for the clinician is to consider the possibility of actinomycosis in time to diagnose it in the least invasive fashion and to avoid unnecessary surgery. Both fine-needle aspiration and biopsy are being used successfully to obtain clinical material for diagnosis, as areCT- and ultrasound-guided aspirations or biopsies. The diagnosis is most commonly made by microscopic identification of sulfur granules (Fig. 166-CD1); occasionally these granules, if sought, can be grossly identified from draining sinus tracts or other purulent material. Although sulfur granules are a defining characteristic of actinomycosis, granules are also found in mycetoma and botryomycosis; however, these entities can easily be differentiated from actinomycosis with appropriate histopathologic and microbiologic studies. Microbiologic identification of actinomycetes is possible in only a minority of cases and is often precluded by prior antimicrobial therapy. Therefore, for optimal yield, the avoidance of even a single dose of antibiotics is mandatory. Primary isolation usually requires 5 to 7 days but may take as long as 2 to 4 weeks. Immunofluorescence testing for *A. israelii*, *A. naeslundii*, and *P. propionicum* (available through the Centers for Disease Control and Prevention in Atlanta) has become a useful diagnostic alternative. Because these organisms are components of the normal oral and genital-tract flora, their identification in sputum, bronchial washings, and cervicovaginal secretions is of little significance in the absence of sulfur granules. *Actinomyces* can be detected in urine by means of appropriate staining and culture.

## TREATMENT

Actinomycosis must be treated with high doses of antimicrobials for a prolonged period. Although therapy needs to be individualized, the intravenous administration of 18 to 24 million units of penicillin for 2 to 6 weeks, followed by oral therapy with penicillin or amoxicillin for 6 to 12 months, is a reasonable guideline for serious infections. Less extensive disease, particularly that involving the oral-cervicofacial region, may require

less intensive therapy. If therapy is extended beyond the point of resolution of measurable disease, the risk of relapse -- a clinical hallmark of this infection -- will be minimized. A similar approach is reasonable for immunocompromised patients, although refractory disease has been described in HIV-infected individuals. Antimicrobial agents whose use is supported by extensive clinical experience are listed inTable 166-1. Although the role played by "companion" microbes in actinomycosis is unclear, many isolates are pathogens in their own right, and a regimen covering these organisms during the initial treatment course is reasonable. Agents whose success has been reported anecdotally are ceftriaxone, ceftizoxime, imipenem, and ciprofloxacin. Drugs that should be avoided are metronidazole, aminoglycosides, oxacillin, dicloxacillin, and cephalexin.

Combined medical-surgical therapy is still advocated by some authorities. However, an increasing body of literature now supports an initial attempt at cure with medical therapy alone, even in extensive disease.CT and magnetic resonance imaging should be used to monitor the response to therapy. Percutaneous drainage is an additional option. When a critical location is involved (e.g., the epidural space, the central nervous system) or when suitable medical therapy fails, surgical intervention may be appropriate.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 167. INFECTIONS DUE TO MIXED ANAEROBIC ORGANISMS - *Dennis L. Kasper*

### DEFINITIONS

*Anaerobic* bacteria are organisms that require reduced oxygen tension for growth, failing to grow on the surface of solid media in 10% $CO_2$ in air. (In contrast, *microaerophilic* bacteria can grow in 10% $CO_2$ in air or under anaerobic or aerobic conditions, although they grow best in the presence of only a small amount of atmospheric oxygen, and *facultative* bacteria can grow in the presence or absence of air.) This chapter describes infections caused by nonsporulating anaerobic bacteria. In general, anaerobes associated with human infections are relatively aerotolerant. They can survive for as long as 72 h in the presence of oxygen, although generally they will not multiply in this environment. A far smaller number of pathogenic anaerobic bacteria (which are also part of the normal flora) die after brief contact with oxygen, even in low concentrations.

The nonsporulating anaerobic bacteria exist as components of the normal flora on the mucosal surfaces of humans and animals. The major reservoirs of these bacteria are the mouth, lower gastrointestinal tract, skin, and female genital tract. Among the constituents of the oral flora, anaerobes are the predominant commensal organisms, ranging in concentration from $10^9$/mL in saliva to $10^{12}$/mL in gingival scrapings. In the oral cavity, the ratio of anaerobic to aerobic bacteria ranges from 1:1 on the surface of a tooth to 1000:1 in the gingival crevice. Anaerobic bacteria are not found in appreciable numbers in the normal upper intestine until the distal ileum. In the colon, the proportion of anaerobes increases significantly, as does the overall bacterial count. For example, in the colon there are $10^{11}$ to $10^{12}$organisms per gram of stool, with a ratio of anaerobes to aerobes of approximately 1000:1. In the female genital tract, there are approximately $10^9$organisms per milliliter of secretions, with a ratio of anaerobes to aerobes of approximately 10:1.

Hundreds of species of anaerobic bacteria have been identified as part of the normal flora of humans. Identification of as many as 500 different anaerobic species in fecal specimens reflects the diversity of the anaerobic flora. Despite the complex array of bacteria in the normal flora, relatively few species are isolated commonly from human infection.

Anaerobic infections occur when the harmonious relationship between the host and the bacteria is disrupted. Any site in the body is susceptible to infection with these indigenous organisms when a mucosal barrier or the skin is compromised by surgery, trauma, tumor, or ischemia or necrosis, which reduce local tissue redox potentials. Because the sites that are colonized by anaerobes contain many species of bacteria, disruption of anatomic barriers allows penetration of many organisms, resulting in mixed infections involving multiple species of anaerobes combined with facultative or microaerophilic organisms. Such mixed infections are seen in the head and neck (chronic sinusitis, chronic otitis media, Ludwig's angina, and periodontal abscesses). Brain abscesses and subdural empyema are the most frequent anaerobic infections of the central nervous system. Anaerobes are responsible for pleuropulmonary diseases such as aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema. These organisms also play an important role in various intraabdominal infections, such

as peritonitis and intraabdominal and liver abscesses (Chap. 130). They are isolated frequently in female genital tract infections, such as salpingitis, pelvic peritonitis, tuboovarian abscess, vulvovaginal abscess, septic abortion, and endometritis (Chaps. 132 and133). Anaerobic bacteria also are frequently found in infections of the skin, soft tissues, and bones and in bacteremia.

## ETIOLOGY

The major anaerobic gram-positive cocci that produce disease are *Peptostreptococcus* spp. The major species involved in infections are *Peptostreptococcus intermedius*, *P. micros*, *P. magnus*, *P. asaccharolyticus*, *P. anaerobius*, and *P. prevotii*. Clostridia are gram-positive rods that are isolated from wounds, abscesses, sites of abdominal infection, and blood; they are discussed inChap. 145. The principal anaerobic gram-negative bacilli found in human infections are the members of the *Bacteroides* "family," which includes the *Bacteroides fragilis* group as well as *Fusobacterium*, *Prevotella*, and *Porphyromonas* spp. Another gram-negative rod, *Bilophila wadsworthia*, has been isolated from infected sites. Gram-positive anaerobic non-spore-forming bacilli are uncommon as etiologic agents of human infections. *Propionibacterium acnes*, a rare cause of foreign body infections, is one of the few non-clostridial gram-positive rods associated with infections.

The *B. fragilis* group contains the anaerobic pathogens most frequently isolated from clinical infections. Members of this group are part of the normal bowel flora; they include several distinct species, such as *B. fragilis*, *B. thetaiotaomicron*, *B. distasonis*, *B. vulgatus*, *B. uniformis*, and *B. ovatus*. (Ribosomal RNA analysis has shown that *B. distasonis* is more closely related to the genus *Porphyromonas* than it is to other *Bacteroides*.) Of this group, *B. fragilis* is the most important clinical isolate. However, *B. fragilis* is isolated from the normal fecal flora in lower numbers than other *Bacteroides* spp.

A second major group of phenotypically similar organisms is part of the indigenous oral flora. Thus these organisms are found at infected sites that can be seeded with oral microflora. Many of these species are pigment-producing bacteria previously classified as *Bacteroides melaninogenicus*. The nomenclature of this group has changed so that two distinct genera, *Prevotella* and *Porphyromonas*, are now recognized; these genera comprise several pathogenic species, including *Porphyromonas gingivalis*, *Porphyromonas asaccharolytica*, and *Prevotella oralis*. *Porphyromonas* and *Prevotella* spp. cause localized infections that can spread contiguously.

In female genital tract infections, organisms normally colonizing the vagina, such as *Prevotella bivia* and *Prevotella disiens*, are the most frequent isolates, although *B. fragilis* is not uncommon. The *Fusobacterium* species *Fusobacterium necrophorum*, *F. nucleatum*, and *F. varium*, which reside primarily in the oral cavity and the gastrointestinal tract, are also isolated from clinical infections, including necrotizing pneumonia and abscesses. *Bilophila wadsworthia* has been reported to cause serious infections, including bacteremia, necrotizing fasciitis, and abscesses; this organism is frequently resistant to several antimicrobials, including imipenem, cefoxitin, and other b-lactam agents.

Infections caused by anaerobic bacteria most frequently are due to more than one organism. These polymicrobial infections may be caused by one or several anaerobic species or by a combination of anaerobic organisms and microaerophilic or facultative bacteria acting synergistically.

### *Approach to the Patient*

The physician must consider several points when approaching the patient with presumptive infection due to anaerobic bacteria.

1. Most of the organisms colonizing mucosal sites are harmless commensals; very few cause disease.

2. For anaerobes to cause tissue infection, they must spread beyond the normal mucosal barriers.

3. Conditions favoring the propagation of these bacteria, particularly a lowered oxidation-reduction potential, are necessary. These conditions exist at sites of trauma, tissue destruction, compromised vascular supply, and complications of preexisting infection, which produce necrosis.

4. There is a complex array of infecting flora. For example, as many as 12 different types of organisms can be isolated from a suppurative site.

5. Anaerobic organisms tend to be found in abscess cavities or in necrotic tissue. The failure of an abscess to yield organisms on routine culture is a clue that the abscess is likely to contain anaerobic bacteria. Often smears of this "sterile pus" are found to be teeming with bacteria when Gram's stain is applied. Malodorous pus suggests anaerobic infection. Although some facultative organisms, such as *Staphylococcus aureus*, are also capable of causing abscesses, abscesses in organs or deeper body tissues should call to mind anaerobic infection.

6. Gas is found in many anaerobic infections of deep tissues.

7. Some species (the best example being the *B. fragilis* group) require specific therapy. However, many synergistic infections can be cured with antibiotics directed at some but not all of the organisms involved. Antibiotic therapy, combined with debridement and drainage, disrupts the interdependent relationship among the bacteria, and some species that are resistant to the antibiotic do not survive without the coinfecting organisms.

8. Manifestations of disseminated intravascular coagulation are unusual in patients with purely anaerobic infection.

## EPIDEMIOLOGY

Difficulties in the performance of appropriate cultures, contamination of cultures by aerobic bacteria or components of the normal flora, and the lack of readily available, reliable culture techniques have made it impossible to obtain accurate incidence or

prevalence data. However, anaerobic infections are encountered frequently in hospitals with active surgical, trauma, and obstetric and gynecologic services. In some centers, anaerobic bacteria, particularly *B. fragilis*, account for approximately 4% of positive blood cultures.

## PATHOGENESIS

Anaerobic bacterial infections usually occur when an anatomic barrier becomes disrupted and constituents of the local flora enter a site that was previously sterile. Because of the specific growth requirements of anaerobic organisms and their presence as commensals on mucosal surfaces, conditions must arise that allow these organisms to penetrate mucosal barriers and enter tissue with a lowered oxidation-reduction potential. Therefore, tissue ischemia, trauma, surgery, perforated viscus, shock, and aspiration provide environments conducive to the proliferation of anaerobes. In the case of a perforated viscus, hundreds of species of anaerobic bacteria are spilled into the peritoneal cavity, but many of these organisms are unable to survive because the highly vascularized tissue provides a sufficiently high redox potential. The entry of oxygen into the environment results in the selection of the more aerotolerant anaerobic organisms.

The ability of an organism to adhere to host tissues is important to the establishment of infection. Some oral species adhere to crevicular epithelium in the oral cavity. *Prevotella melaninogenica* actually attaches to other microorganisms; *P. gingivalis* is a common isolate in periodontal disease. These organisms have fimbriae that facilitate attachment. Some unencapsulated *Bacteroides* strains appear to be piliated, a characteristic that may account for their ability to adhere.

The most extensively studied virulence factor of the nonsporulating anaerobes is the polysaccharide capsule of *B. fragilis*. This polysaccharide possesses distinct biologic properties, such as the ability (owing to a unique zwitterionic motif of charged sugars) to promote abscess formation. Intraabdominal abscess induction is related to the capacity of the polysaccharide to stimulate the release of cytokines, in particular interleukin 8 (IL-8) and tumor necrosis factora (TNF-a), from resident peritoneal cells. IL-8 results in the chemotaxis of polymorphonuclear neutrophils (PMNs) into the peritoneum, where they adhere to mesothelial cells induced by TNF-a to upregulate their expression of intercellular adhesion molecule 1 (ICAM-1). PMNs adherent to ICAM-1-expressing cells probably represent the nidus for an abscess. Prophylactic or therapeutic administration of the polysaccharide or a zwitterionic mimetic to experimental animals confers protection against abscess induction following challenge with intestinal microorganisms capable of inducing abscesses. This protection is mediated by T cells controlling cytokine release, which blocks the tissue response of abscess formation. Although abscesses constitute a host response that localizes and contains infecting bacteria, abscess formation in patients with sepsis often results in severe and chronic illness that requires surgical drainage in combination with antimicrobial therapy.

Anaerobic bacteria produce a number of exoproteins that are capable of enhancing the organisms' virulence. The collagenase produced by *P. gingivalis* may enhance tissue destruction. An enterotoxin has been identified in *B. fragilis* strains associated with diarrheal disease in animals and young children. This 20-kDa zinc-dependent metalloprotease reversibly alters the morphology of the tight junctional complexes of

intestinal epithelial cells. Both *B. fragilis* and *P. melaninogenica* possess lipopolysaccharides (endotoxins) that are less biologically potent than endotoxins associated with aerobic gram-negative bacteria. This relative biologic inactivity may account for the lower frequency of disseminated intravascular coagulation and purpura in *Bacteroides* bacteremia than in facultative and aerobic gram-negative bacillary bacteremia.

## CLINICAL MANIFESTATIONS

**Anaerobic Infections of the Mouth, Head, and Neck (See alsoChap. 30)** Infections of the mouth can arise from either the supragingival or the subgingival dental plaque. Supragingival plaque formation begins with the adherence of gram-positive bacteria to the tooth surface. This form of plaque is influenced by salivary and dietary components, oral hygiene, and local host factors. Once the supragingival plaque is established, the acquisition of pathogenic bacteria and an increase in the amount of plaque are responsible for the ultimate development of gingivitis. Early bacteriologic changes in the supragingival plaque initiate an inflammatory response in the gingiva, including edema, swelling, and increased gingival fluid, and cause the development of caries and endodontic (pulp) infections. In addition, these changes contribute to the subsequent pathogenic alteration in the subgingival plaque that arises from poor or inadequate oral hygiene.

Subgingival plaque is associated with periodontal disease and disseminated infection arising from the oral cavity. Bacteria that colonize the subgingival area are primarily anaerobic. The black-pigmented gram-negative anaerobic bacilli, principally *P. gingivalis* and *P. melaninogenica*, are the most important. Infections in this area are frequently mixed and involve both anaerobic and aerobic bacteria. After establishment of local infection either in root canals or in the periodontal area, infection may extend into the mandible, causing osteomyelitis to the maxillary sinuses; or to local tissues in the submandibular or submental spaces, depending on which teeth are involved. Periodontitis also may result in spreading infection that can involve adjacent bone or soft tissues.

*Gingivitis* Gingivitis may become a necrotizing infection (trench mouth, Vincent's stomatitis). The onset of disease is usually sudden and is associated with tender bleeding gums, foul breath, and a bad taste. The gingival mucosa, especially the papillae between the teeth, becomes ulcerated and may be covered by a gray exudate, which is removable with gentle pressure. Patients may become systemically ill, developing fever, cervical lymphadenopathy, and leukocytosis. Occasionally, ulcerative gingivitis can spread to the buccal mucosa, the teeth, and the mandible or maxilla, resulting in widespread destruction of bone and soft tissue. This infection is termed *acute necrotizing ulcerative mucositis* (cancrum oris, noma). It destroys tissue rapidly, causing the teeth to fall out and large areas of bone -- or even the whole mandible -- to be sloughed. A strong putrid odor is frequently detected, although the lesions are not painful. The gangrenous lesions eventually heal, leaving large disfiguring defects. This infection is seen most commonly following a debilitating illness or in severely malnourished children. It has been known to complicate leukemia or to develop in individuals with a genetic deficiency of catalase.

*Acute Necrotizing Infections of the Pharynx* These infections usually occur in association with ulcerative gingivitis. Symptoms include an extremely sore throat, foul breath, and a bad taste accompanied by fever and a sensation of choking. Examination of the pharynx demonstrates that the tonsillar pillars are swollen, red, ulcerated, and covered with a grayish membrane that peels easily. Lymphadenopathy and leukocytosis are common. The disease may last for only a few days or, if not treated, may persist for weeks. Lesions begin unilaterally but may spread to the other side of the pharynx or the larynx. Aspiration of the infected material by the patient can result in lung abscesses. Soft tissue infection of the oral-facial area may or may not be odontogenic. *Ludwig's angina*, a periodontal infection usually arising from the tissues surrounding the third molar, may produce submandibular cellulitis that results in marked local swelling of tissues, with pain, trismus, and superior and posterior displacement of the tongue. Submandibular swelling of the neck can impair swallowing and cause respiratory obstruction. In some cases, tracheotomy may be life-saving.

*Fascial Infections* These infections arise from the spread of organisms originating in the upper airways to potential spaces formed by the fascial planes of the head and neck. Perimandibular space infection most commonly involves the submandibular, peritonsillar, and parapharyngeal spaces. Peritonsillar abscesses occur in association with pharyngitis. Complicated dental infections spread to the submandibular and buccal spaces. Entry of organisms by either portal can result in parapharyngeal space infections. Although there are few well-documented reports on the microbiology of these syndromes, anaerobes from the oral flora have been implicated in many cases. Fascial infections associated with *S. aureus* or *Streptococcus pyogenes* may arise from boils or impetigo, whereas anaerobes are associated with space infections either occurring spontaneously or arising from diseases of the mucous membranes or from dental manipulations.

*Sinusitis and Otitis* The role of anaerobic bacteria in acute sinusitis may be underestimated because of improper collection of specimens. In a study of chronic sinusitis, anaerobic bacteria were found in 52% of specimens collected during external frontoethmoidotomy or radical antrotomy. Anaerobic bacteria are much more easily implicated in chronic suppurative otitis media than in acute otitis media. Purulent exudate from chronically draining ears has been found to contain anaerobes, particularly *Bacteroides* spp., in up to 50% of cases. *B. fragilis* has been isolated from up to 28% of patients with chronic otitis media.

*Complications of Anaerobic Head and Neck Infections* Contiguous craniad spread of these infections may result in osteomyelitis of the skull or mandible or in intracranial infections such as brain abscess and subdural empyema. Caudad spread can produce mediastinitis or pleuropulmonary infection. Hematogenous complications may also result from anaerobic infections of the head and neck. Bacteremia, which occasionally is polymicrobial, can lead to endocarditis or other distant infections. When infections spread to produce suppurative thrombophlebitis of the internal jugular vein, a destructive syndrome (*Lemierre's*) -- with prolonged fever, bacteremia, septic emboli to both the lung and the brain, and multiple metastatic foci of suppurative infection -- may develop. This syndrome has been reported with fusobacterial septicemia following exudative pharyngitis but has been uncommon in the antimicrobial era.

**Central Nervous System Infections** Brain abscesses are frequently associated with anaerobic bacteria (Chap. 372). If optimal bacteriologic techniques are employed, as many as 85% of brain abscesses yield anaerobic bacteria -- most often anaerobic gram-positive cocci (especially peptostreptococci), which are followed in frequency by *Fusobacterium* and *Bacteroides* spp. Facultative or microaerophilic streptococci and coliforms often are part of a mixed infecting flora in brain abscesses.

**Pleuropulmonary Infections** Anaerobic pleuropulmonary infections result from the aspiration of oropharyngeal contents, often in the context of an altered state of consciousness or an absent gag reflex. Four clinical syndromes are associated with anaerobic pleuropulmonary infection produced by aspiration: simple aspiration pneumonia, necrotizing pneumonia, lung abscess, and empyema.

*Aspiration Pneumonitis* Aspiration pneumonitis must be distinguished from two other clinical syndromes associated with aspiration that are not of bacterial etiology. One syndrome results from aspiration of solids, usually food. Obstruction of major airways typically results in atelectasis and moderate nonspecific inflammation. Therapy consists of removal of the foreign body.

The second aspiration syndrome is more easily confused with bacterial aspiration. *Mendelson's* syndrome results from regurgitation of stomach contents and aspiration of chemical material, usually gastric juices. Pulmonary inflammation -- including the destruction of the alveolar lining, with transudation of fluid into the alveolar space -- occurs with remarkable rapidity. Typically this syndrome develops within hours, often following anesthesia when the gag reflex is depressed. The patient becomes tachypneic, hypoxic, and febrile. The leukocyte count may rise, and the chest x-ray may evolve suddenly from normal to a complete bilateral "whiteout" within 8 to 24 h. Sputum production is minimal. The pulmonary signs and symptoms can resolve quickly with symptom-based therapy or can culminate in respiratory failure, with the subsequent development of bacterial superinfection over a period of days. Antibiotic therapy is not indicated unless bacterial infection supervenes. The signs of bacterial infection include sputum production, persistent fever, leukocytosis, and clinical evidence of sepsis.

In contrast to these syndromes, bacterial aspiration pneumonia develops more slowly. It is seen in patients who are hospitalized and have a depressed gag reflex, impaired swallowing, or a tracheal or nasogastric tube; elderly patients; or those with transiently impaired consciousness in the wake of seizures, cerebrovascular accidents, or alcoholic blackouts. Patients who enter the hospital with this syndrome typically have been ill for several days and generally report low-grade fever, malaise, and sputum production. Usually the history reveals factors predisposing to aspiration, such as alcohol overdose or residence in a nursing home. Sputum characteristically is not malodorous unless the process has been under way for at least a week. A mixed bacterial flora with many PMNs is evident on Gram's staining; cultures are reliable only if contamination with the normal oral flora is avoided -- that is, if specimens are obtained by transtracheal aspiration. In general, this procedure is not indicated in the evaluation of these patients. The most commonly encountered anaerobes in these infections are pigmented and nonpigmented *Prevotella* spp., *F. nucleatum*, *Peptostreptococcus* spp., and *Bacteroides* spp. Chest x-rays show consolidation in dependent pulmonary segments: in the basilar segments of the lower lobes if the patient has aspirated while upright and in either the

posterior segment of the upper lobe (usually on the right side) or the superior segment of the lower lobe if the patient has aspirated while supine. The organisms isolated reflect the pharyngeal flora; *P. melaninogenica*, *Fusobacterium* spp., and anaerobic cocci are the most frequent isolates. The patient who aspirates in the hospital also may have a mixed infection involving enteric gram-negative rods.

*Necrotizing Pneumonitis* This form of anaerobic pneumonitis is characterized by numerous small abscesses that spread to involve several pulmonary segments. The process can be indolent or fulminating. This syndrome is less common than either aspiration pneumonia or lung abscess and includes features of both types of infection.

*Anaerobic Lung Abscesses (Fig. 167-CD1)* These abscesses result from subacute anaerobic pulmonary infection. The clinical syndrome typically involves a history of constitutional symptoms, including malaise, weight loss, fever, chills, and foul-smelling sputum, perhaps over a period of weeks (Chap. 255). Patients who develop lung abscesses characteristically have dental infection and periodontitis, but lung abscesses in edentulous patients have been reported. Abscess cavities may be single or multiple and generally occur in dependent pulmonary segments. Anaerobic abscesses must be distinguished from those associated with tuberculosis, neoplasia, and other conditions. Oral anaerobes predominate, although *B. fragilis* is isolated in up to 10% of cases. *S. aureus* may be found as well.

*Empyema* Empyema is a manifestation of long-standing anaerobic pulmonary infection. The clinical presentation, which includes the presence of foul-smelling sputum, resembles that of other anaerobic pulmonary infections. Patients may report pleuritic chest pain and marked chest-wall tenderness.

Empyema may be masked by overlying pneumonitis and should be considered especially in cases of persistent fever despite antibiotic therapy. Diligent physical examination and the use of ultrasound to localize a loculated empyema are important diagnostic tools. The collection of a foul-smelling exudate by thoracentesis is typical. Cultures of infected pleural fluid yield an average of 3.5 anaerobes and 0.6 facultative or aerobic bacterial species. Drainage is required. Defervescence, a return to a feeling of well-being, and resolution of the process may require several months.

Extension from a subdiaphragmatic infection also may result in anaerobic empyema. Septic pulmonary emboli may originate from intraabdominal or female genital tract infections and can produce anaerobic pneumonia.

**Intraabdominal Infections** Enterotoxigenic *B. fragilis* has been associated with watery diarrhea in a small number of young children and adults. In case-control studies of children with undiagnosed diarrheal disease, enterotoxigenic *B. fragilis* was isolated from significantly more children with diarrhea than children in the control group. This organism may play a role in a small proportion of childhood diarrhea cases. Neutropenic enterocolitis (typhlitis) has been associated with anaerobic infection of the cecum but -- in the setting of neutropenia (Chap. 85) -- may involve the entire bowel. Patients usually present with fever; abdominal pain, tenderness, and distension; and watery diarrhea. The bowel wall is edematous with hemorrhage and necrosis. The primary pathogen is thought by some authorities to be *C. septicum*, but other clostridia and mixed anaerobic

infections have also been implicated. More than 50% of patients developing early clinical signs can benefit from antibiotic therapy and bowel rest. Surgery is sometimes required to remove gangrenous bowel.*See Chap. 130 for a complete discussion of intraabdominal infections.*

**Pelvic Infections** The vagina of a healthy woman is one of the major reservoirs of anaerobic and aerobic bacteria. In the normal flora of the female genital tract, anaerobes outnumber aerobes by a ratio of approximately 10:1 and include anaerobic gram-positive cocci and *Bacteroides* spp. Anaerobes are isolated from most patients with genital tract infections not caused by a sexually transmitted pathogen. The major anaerobic pathogens are *B. fragilis*, *P. bivia*, *P. disiens*, *P. melaninogenica*, anaerobic cocci, and *Clostridium* spp. Anaerobes frequently are encountered in tuboovarian abscess, septic abortion, pelvic abscess, endometritis, and postoperative wound infection, particularly following hysterectomy. Although these infections are frequently mixed, involving both anaerobes and coliforms, pure anaerobic infections without coliform or other facultative bacterial species occur more often in pelvic than in intraabdominal sites and are characterized by drainage of foul-smelling pus or blood from the uterus, generalized uterine or local pelvic tenderness, and continued fever and chills. Suppurative thrombophlebitis of the pelvic veins may complicate the infections and lead to repeated episodes of septic pulmonary emboli.

Anaerobic bacteria have been thought to be contributing factors in the etiology of *bacterial vaginosis*. This syndrome of unknown etiology is characterized by a profuse malodorous discharge and an increase in the number of bacteria in the vagina, including *Gardnerella vaginalis*, *Prevotella* spp., *Mobiluncus* spp., peptostreptococci, and genital mycoplasmas. Anaerobic bacteria are thought to play a role in the etiology of pelvic inflammatory disease (Chap. 133), and several investigations have shown an association between bacterial vaginosis and the development of pelvic inflammatory disease.

Pelvic infections due to *Actinomyces* spp. have been associated with use of intrauterine devices (Chap. 166).

**Skin and Soft Tissue Infections** Injury to skin, bone, or soft tissue by trauma, ischemia, or surgery creates a suitable environment for anaerobic infections. These infections are most frequently found in sites prone to contamination with feces or with upper airway secretions -- for example, wounds associated with intestinal surgery, decubitus ulcers, or human bites. Anaerobic bacteria can be isolated in cases of crepitant cellulitis, synergistic cellulitis, or gangrene and necrotizing fasciitis (Chaps. 128 and145). Moreover, these organisms have been isolated from cutaneous abscesses, rectal abscesses, and axillary sweat gland infections (hydradenitis suppurativa). Anaerobes are frequently cultured from foot ulcers in diabetic patients.

These soft tissue or skin infections are usually polymicrobial. A mean of 4.8 bacterial species are isolated, with a roughly 3:2 ratio of anaerobes to aerobes. The most frequently isolated organisms include *Bacteroides* spp., *Peptostreptococcus* spp., enterococci, *Clostridium* spp., and *Proteus* spp. The involvement of anaerobes in these types of infections is associated with a higher frequency of fever, foul-smelling lesions, gas in the tissues, or visible foot ulcer.

Anaerobic bacterial *synergistic gangrene* (*Meleney's gangrene*) is characterized by exquisite pain, redness, and swelling followed by induration. Erythema surrounds a central zone of necrosis. A granulating ulcer forms at the original center as necrosis and erythema extend outward. Symptoms are limited to pain; fever is not typical. These infections usually involve a combination of *Peptostreptococcus* spp. and *S. aureus*; the usual site of infection is an abdominal surgical wound or the area surrounding an ulcer on an extremity. Treatment includes surgical removal of necrotic tissue and antimicrobial administration.

*Necrotizing fasciitis*, a rapidly spreading destructive disease of the fascia, is usually attributed to group A streptococci but can also be caused by anaerobic bacteria, including *Peptostreptococcus* and *Bacteroides* spp. Gas may be found in the tissues. Similarly, myonecrosis can be associated with mixed anaerobic infection. *Fournier's gangrene* consists of cellulitis involving the scrotum, perineum, and anterior abdominal wall, with mixed anaerobic organisms spreading along deep external fascial planes and causing extensive loss of skin.

**Bone and Joint Infections** Although *actinomycosis* (Chap. 166) accounts on a worldwide basis for most anaerobic infections in bone, organisms including *Peptostreptococcus* spp. or microaerophilic cocci, *Bacteroides* spp., *Fusobacterium* spp., and *Clostridium* spp. can also be found. These infections frequently arise adjacent to soft tissue infections. Hematogenous seeding of bone is uncommon. *Prevotella* and *Porphyromonas* spp. are detected in infections involving the maxilla and mandible, whereas *Clostridium* spp. have been reported as anaerobic pathogens in cases of osteomyelitis of the long bones following fracture or trauma. Fusobacteria have been isolated in pure culture from sites of osteomyelitis adjacent to the perinasal sinuses. *Peptostreptococcus* spp. and microaerophilic cocci have been reported as significant pathogens in infections involving the skull, mastoid, and prosthetic implants placed in bone. In patients with osteomyelitis (Chap. 129), the most reliable culture specimen is a bone biopsy sample free of normal uninfected skin and subcutaneous tissue. In patients with anaerobic osteomyelitis, a mixed flora is frequently isolated from a bone biopsy specimen.

In cases of anaerobic septic arthritis, the most common isolates are *Fusobacterium* spp. Most of the patients involved have uncontrolled peritonsillar infections progressing to septic cervical venous thrombophlebitis and resulting in hematogenous dissemination with a predilection for the joints. Unlike anaerobic osteomyelitis, anaerobic pyoarthritis in most cases is not polymicrobial and may be acquired hematogenously. Anaerobes are important pathogens in infections involving prosthetic joints; in these infections, the causative organisms (such as *Peptostreptococcus* spp. and *P. acnes*) are part of the normal skin flora.

**Bacteremia** Transient bacteremia is a well-known event in healthy people whose anatomic mucosal barriers have been injured (e.g., during dental extractions or dental scaling). These bacteremic episodes, which are often due to anaerobes, have no pathologic consequences. However, anaerobic bacteria are found in cultures of blood from clinically ill patients when proper culture techniques are used. *B. fragilis* is the single most common anaerobic isolate from the bloodstream.

In recent years, the rate of isolation of anaerobic bacteria from blood cultures has been decreasing. Studies from the 1970s and early 1980s found that 10 to 15% of positive blood cultures yielded anaerobes, while more recent surveys have found rates as low as 4%. The cause of this change is unknown but may be related to the administration of antibiotic prophylaxis before intestinal surgery, the earlier recognition of localized infections, and the empirical use of broad-spectrum antibiotics for presumed infection.

Once the organism has been identified, both the portal of bloodstream entry and the underlying problem that probably led to seeding of the bloodstream can often be deduced from an understanding of the organism's normal site of residence. For example, mixed anaerobic bacteremia including *B. fragilis* usually implies colonic pathology with mucosal disruption from neoplasia, diverticulitis, or some other inflammatory lesion. The initial manifestations are determined by the portal of entry and reflect the localized condition. When bloodstream invasion occurs, patients can become extremely ill, with rigors and hectic fevers ranging up to 40.6°C (105°F). The clinical picture may be quite similar to that seen in sepsis involving aerobic gram-negative bacilli. Although other complications of anaerobic bacteremia, such as septic thrombophlebitis and septic shock, have been reported, the incidence of these complications in association with anaerobic bacteremia is low. Anaerobic bacteremia is potentially fatal and requires rapid diagnosis and appropriate therapy. Mortality appears to increase with the age of the patient (with reported rates of more than 66% among patients over 60 years old), with the isolation of multiple species from the bloodstream, and with the failure to surgically remove a focus of infection.

**Endocarditis and Pericarditis (See also Chap. 126)** Endocarditis due to anaerobes is uncommon. However, anaerobic streptococci, which are often classified incorrectly, are responsible for this disease more frequently than is generally appreciated. Gram-negative anaerobes are unusual causes of endocarditis. Anaerobes, particularly *B. fragilis* and *Peptostreptococcus* spp., are uncommonly found in infected pericardial fluids. Anaerobic pericarditis is associated with a mortality rate of>50%.

## DIAGNOSIS

Because of the time and difficulty involved in the isolation of anaerobic bacteria, diagnosis of anaerobic infections must frequently be based on presumptive evidence. Certain sites (such as avascular necrotic tissues) with lowered oxidation-reduction potential favor the diagnosis of an anaerobic infection. When infections occur in proximity to mucosal surfaces normally harboring an anaerobic flora, such as the gastrointestinal tract, female genital tract, or oropharynx, anaerobes should be considered as potential etiologic agents. A foul odor is often indicative of anaerobes, which produce certain organic acids as they proliferate in necrotic tissue. Although these odors are nearly pathognomonic for anaerobic infection, the absence of odor does not exclude an anaerobic etiology. Because anaerobes often coexist with other bacteria to cause mixed or synergistic infection, Gram's staining of exudate frequently reveals numerous pleomorphic cocci and bacilli suggestive of anaerobes. Sometimes these organisms have morphologic characteristics associated with specific species.

The presence of gas in tissues is highly suggestive, but not diagnostic, of anaerobic

infection. When cultures of obviously infected sites yield no growth, streptococci only, or a single aerobic species (such as *Escherichia coli*) and Gram's staining reveals a mixed flora, the implication is that the anaerobic microorganisms failed to grow because of inadequate transport and/or culture techniques. Failure of a patient to respond to antibiotics that are not active against anaerobes -- for example, aminoglycosides and in some circumstances penicillin, cephalosporins, or tetracyclines -- suggests anaerobic infection.

There are three critical steps in the diagnosis of anaerobic infection: (1) proper specimen collection; (2) rapid transport of the specimens to the microbiology laboratory, preferably in anaerobic transport media; and (3) proper handling of the specimens by the laboratory. Specimens must be collected by meticulous sampling of infected sites, with avoidance of contamination by the normal flora. When such contamination is likely, the specimen is unacceptable. Examples of specimens unacceptable for anaerobic culture include sputum collected by expectoration or nasal tracheal suction, bronchoscopy specimens, samples collected directly through the vaginal vault, urine collected by voiding, and feces. Specimens that can be cultured for anaerobes include blood, pleural fluid, transtracheal aspirates, pus obtained by direct aspiration from an abscess cavity, fluid obtained by culdocentesis, suprapubic bladder aspirates, cerebrospinal fluid, and lung puncture specimens.

Because even brief exposure to oxygen may kill some anaerobic organisms and result in failure to isolate them in the laboratory, air must be expelled from the syringe used to aspirate the abscess cavity, and the needle must be capped with a sterile rubber stopper. Proper precautions should be used in the handling of contaminated needles. Specimens can be injected into transport bottles containing a reduced medium or taken immediately in syringes to the laboratory for direct culture on anaerobic media. In general, swabs should not be used. If a swab must be used, it should be placed in a reduced semisolid carrying medium before transport to the laboratory. Delays in transport may lead to a failure to isolate anaerobes due to exposure to oxygen or overgrowth of facultative organisms, which may eliminate or obscure any anaerobes that are present. All clinical specimens from suspected anaerobic infections should be Gram-stained and examined for organisms with characteristic morphology (Fig. 167-CD2). It is not unusual for organisms to be observed on Gram's staining but not isolated in culture. If purulent materials are found to be sterile or organisms are seen on Gram's staining but do not grow in the culture, the involvement of anaerobes should be suspected.

## TREATMENT

Successful therapy for anaerobic infections requires the administration of a combination of appropriate antibiotics, surgical resection, debridement of devitalized tissues, and drainage. Perforations must be closed promptly, closed spaces drained, tissue compartments decompressed, and an adequate blood supply established. Abscess cavities should be drained as soon as fluctuation or localization occurs. Surgery was formerly required to establish drainage; however, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound now allow diagnostic radiologists to drain many abscess sites percutaneously.

**Antibiotic Therapy and Resistance** Decisions about the treatment of anaerobic infections with antibiotics are usually based on known resistance patterns in certain species, on the likelihood of encountering a given species in the case at hand, and on Gram's stain findings. Antibiotics active against *Bacteroides* spp., penicillin-resistant *Prevotella* and *Porphyromonas* spp., and *Fusobacterium* spp. can be grouped into four categories on the basis of their predicted activity against anaerobes (Table 167-1). (Nearly all the drugs listed have toxic side effects, which are described in detail inChap. 137.) In many infections, anaerobes are mixed with coliforms and other facultative organisms. The best therapeutic regimens, therefore, are usually those active against both aerobic and anaerobic bacteria. The choice of empirical antibiotics for the anaerobes in mixed infections can nearly always be made reliably, since patterns of antimicrobial susceptibility are usually predictable (Chap. 137 andTable 167-1).

Antibiotic susceptibility testing of anaerobic bacteria has been difficult and controversial. Owing to the slow growth rate of many anaerobes, the lack of standardized testing methods and of clinically relevant standards for resistance, and the generally good results obtained with empirical therapy, susceptibility testing has been recommended only for the study of local or regional resistance patterns, for the prediction of the efficacy of new antibiotics, and for the management of selected patients.

Anaerobic gram-negative rods that are frequently resistant to penicillin are listed inTable 167-2. Clinically important *Bacteroides* spp. are essentially all resistant to penicillin. Failures of therapy are common when documented *Bacteroides* (especially *B. fragilis*) infection is treated with penicillin or first-generation cephalosporins. The number of antimicrobial agents effective against *Bacteroides* spp. has expanded, and there are currently several useful choices (Table 167-1). In general, cure rates of>80% can be attained in patients with *Bacteroides* infection by means of appropriate antimicrobial therapy and drainage.

Resistance to metronidazole has been reported only rarely in *Bacteroides* spp. This well-tolerated drug, which reaches significant levels in serum and also can be found at high concentrations in abscess cavities, should be considered first-line therapy against *Bacteroides* infection. However, if metronidazole is used to treat mixed anaerobic and aerobic infections, it is imperative that other appropriate antibiotics be used in conjunction. Metronidazole is inactive against aerobic and facultative bacteria, *Actinomyces* spp., and *Propionibacterium* spp. The sensitivity of peptostreptococci to metronidazole is unpredictable, and penicillin remains the drug of choice.

If a patient fails to respond to one of the group 1 or group 2 drugs (Table 167-1), consideration should be given to alternative therapy and to determination of the resistance patterns among *Bacteroides* isolates. Although in vitro resistance of *Bacteroides* spp. to chloramphenicol has not been reported, this drug may not be as effective as other group 1 drugs. Ampicillin/sulbactam, ticarcillin/clavulanic acid, piperacillin/tazobactam, imipenem, and meropenem have been effective in the treatment of *B. fragilis* infection. Some newer fluoroquinolones, such as clinafloxacin, appear to be highly active against most anaerobes, including *B. fragilis*; however, ciprofloxacin and other earlier-generation quinolones should not be used as primary agents.

**Treatment of Infections at Specific Sites** In clinical situations, specific regimens must be tailored to the initial site of infection. The duration of therapy also depends on the infection site; the reader is referred to specific chapters on sites of infection for recommendations.

b-Lactamase production has been reported in anaerobic strains that are usually isolated from infections originating above the diaphragm. Up to 60% of clinical isolates classified as *Prevotella* or *Porphyromonas* spp., non-*B. fragilis* species of *Bacteroides*, or *Fusobacterium* spp. reportedly produceb-lactamase (Table 167-2). The clinical significance of resistance in these organisms has been suggested by studies showing clindamycin to be superior to penicillin (which for many years was considered the therapeutic gold standard) for the treatment of lung abscesses. Presumably, the success of clindamycin is attributable to a broader spectrum of activity against oral anaerobes; thus, a combination of penicillin and metronidazole or another antibiotic combination that is active against both oral anaerobes and aerobes is likely to be as effective as clindamycin. Bronchoscopy in lung abscess is indicated only to rule out airway obstruction and does not enhance drainage; in any event, it should be delayed until the antimicrobial regimen has begun to affect the disease process so that the procedure does not spread the infection. Surgery is almost never indicated because of the danger of spilling the abscess contents into the lungs.

Although most oral anaerobic infections and most cases of anaerobic pneumonia still respond to penicillin therapy, some infections due to oral organisms fail to respond to this drug, and in these cases the use of a drug that is effective against penicillin-resistant anaerobes is recommended (Table 167-1). Life-threatening infections involving the anaerobic flora of the mouth, such as space infections of the head and neck, should be treated empirically as if penicillin-resistant anaerobes are involved. Less serious infections involving the oral microflora can be treated with penicillin alone; metronidazole can be added (or clindamycin can be substituted) if the patient responds poorly to penicillin therapy. Combinations of antibiotics used to treat mixed infections of oral origin must include drugs active against the gram-positive aerobic flora of the mouth.

Chloramphenicol has been used successfully against anaerobic central nervous system infections at doses of 30 to 60 mg/kg per day, with the exact dose depending on the severity of illness. However, penicillin G and metronidazole also cross the blood-brain barrier and are bactericidal for many anaerobic organisms (Chap. 372).

Anaerobic infections arising below the diaphragm (e.g., colonic and intraabdominal infections) must be treated specifically with agents active against *Bacteroides* spp. (see Table 167-1). In intraabdominal sepsis (Chap. 130), the use of antibiotics effective against penicillin-resistant anaerobes has clearly reduced the incidence of postoperative infections and serious infectious complications. Specifically, a drug from group 1 (Table 167-1) must be included for broad-spectrum coverage. Recommended doses for commonly used group 1 drugs are given inTable 167-3. Therapy for intraabdominal sepsis also must include drugs active against the gram-negative aerobic flora of the bowel. If the involvement of gram-positive bacteria such as enterococci is suspected, either ampicillin or vancomycin should be added.

Cases of anaerobic osteomyelitis in which a mixed flora is isolated from a bone biopsy specimen should be treated with a regimen that covers all the isolates. When an anaerobic organism is recognized as a major or sole pathogen infecting a joint, the duration of treatment should be similar to that used for arthritis caused by aerobic bacteria (Chap. 323). Therapy includes the management of underlying disease states, the administration of appropriate antimicrobial agents, temporary joint immobilization, percutaneous drainage of effusions, and usually the removal of infected prostheses or internal fixation devices. Surgical drainage and debridement procedures such as sequestrectomy are essential for the removal of necrotic tissue that can sustain anaerobic infections.

The outcome of anaerobic bacteremia has been shown to be significantly better in patients either initially given or switched to appropriate therapy based on known antibiotic susceptibilities.

**Failure of Therapy** Anaerobic infections that fail to respond to treatment or that relapse should be reassessed. Consideration should be given to additional surgical drainage or debridement. Superinfections with resistant gram-negative facultative or aerobic bacteria should be ruled out. The possibility of drug resistance must be entertained; if resistance is involved, repeated cultures may yield the pathogenic organism.

**Supportive Measures** Other supportive measures in the management of anaerobic infections include careful attention to fluid and electrolyte balance (since extensive local edema may lead to hypoalbuminemia); hemodynamic support for septic shock; immobilization of infected extremities; maintenance of adequate nutrition during chronic infections by parenteral hyperalimentation; relief of pain; and anticoagulation with heparin for thrombophlebitis. For patients with severe anaerobic infections of soft tissues, hyperbaric oxygen therapy is advocated by some experts, but its value has not been proven in controlled trials.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 8 -MYCOBACTERIAL DISEASES

# 168. ANTIMYCOBACTERIAL AGENTS - *Paul W. Wright*, *Richard J. Wallace, Jr.*

The physician is greatly challenged to provide optimal therapy for mycobacterial illnesses because of the advent of AIDS, the increase in both drug-susceptible and multidrug-resistant tuberculosis, and the plethora of new antibiotics with antimycobacterial potential. This chapter reviews the agents used for the treatment of tuberculosis, leprosy (Hansen's disease), and diseases caused by pathogenic nontuberculous mycobacteria, including *Mycobacterium avium-intracellulare*, *M. kansasii*, the rapidly growing mycobacteria, and *M. marinum*. The use of antimycobacterial agents in patients with renal or hepatic disease and in pregnant women is summarized inTable 168-1. The effects of major antimycobacterial agents on the levels, activity, and toxicity of other commonly used drugs are summarized in Table 168-2.

## TUBERCULOSIS

Drugs used to treat tuberculosis are classified as first-line and second-line agents. *First-line essential* antituberculous agents are the most effective and are a necessary component of any short-course therapeutic regimen. The three drugs in this category are rifampin, isoniazid, and pyrazinamide. The *first-line supplemental* agents, which are highly effective and infrequently toxic, include ethambutol and streptomycin. *Second-line* antituberculous drugs are clinically much less effective than first-line agents and much more frequently elicit severe reactions. These drugs are rarely used in therapy and then only by caregivers experienced with their use. They include para-aminosalicylic acid (PAS), ethionamide, cycloserine, kanamycin, amikacin, capreomycin, viomycin, and thiacetazone. *Newer* antituberculous drugs, which have not yet been placed in the above categories, include rifapentine, rifabutin, and the quinolones, especially ciprofloxacin, ofloxacin, and sparfloxacin.

### FIRST-LINE ESSENTIAL DRUGS

**Rifampin** Rifampin, a semisynthetic derivative of *Streptomyces mediterranei*, is considered the most important and potent antituberculous agent. It is also active against a wide spectrum of other organisms, including some gram-positive and gram-negative bacteria, *Legionella* spp., *M. kansasii*, and *M. marinum*.

*Pharmacology* Rifampin is a fat-soluble complex macrocyclic antibiotic that is absorbed readily after either oral or intravenous administration. Serum levels of 10 to 20 ug/mL follow a standard oral dose of 600 mg. Rifampin distributes well throughout most body tissues, including inflamed meninges. The fact that rifampin turns body fluids (urine, saliva, sputum, tears) to a red-orange color makes it simple and inexpensive to check on a patient's compliance with therapy. Rifampin is excreted primarily through the bile and the enterohepatic circulation, while 30 to 40% of a dose is excreted via the kidneys. The drug is administered either twice weekly or daily at a dose of 600 mg for adults (10 mg/kg) and 10 to 20 mg/kg for children.

*Mechanism of action* Rifampin has both intracellular and extracellular bactericidal

activity. It blocks RNA synthesis by specifically binding and inhibiting DNA-dependent RNA polymerase. Susceptible strains of *M. tuberculosis* as well as *M. kansasii* and *M. marinum* are inhibited by£1 ug/mL.

*Adverse effects (Table 168-3)* Rifampin is generally well tolerated; the most common adverse event is gastrointestinal upset. Patients with chronic liver disease, especially those with alcoholism and the elderly, appear to be at unusually high risk for the most serious adverse reaction: hepatitis. Other adverse effects of rifampin include rash (0.8%), hemolytic anemia (<1%), thrombocytopenia, and immunosuppression of unknown clinical importance. Rifampin is a potent inducer of the hepatic microsomal enzymes and thereby decreases the half-life of a number of drugs, including digoxin, warfarin, prednisone, cyclosporine, methadone, oral contraceptives, clarithromycin, the HIV protease inhibitors, and quinidine (Table 168-2).

*Resistance* Resistance to rifampin results from spontaneous point mutations that alter theb subunit of the RNA polymerase (*rpoB*) gene. Studies have shown that 96% of rifampin-resistant strains have a missense mutation within a 91-bp central core region of the gene. Rifampin-resistant strains of *M. leprae* have similar mutations that alter a single serine residue (Ser-425) in the same core region of the *rpoB* gene.

**Isoniazid** Now considered the best antituberculous drug available after rifampin, isoniazid should be included in all tuberculosis treatment regimens unless the organism is resistant. Isoniazid is inexpensive, readily synthesized, available worldwide, highly selective for mycobacteria, and well tolerated, with only 5% of patients exhibiting adverse effects.

*Mechanism of Action* Isoniazid is the hydrazide of isonicotinic acid, a small water-soluble molecule that easily penetrates the cell. Its mechanism of action involves inhibition of mycolic acid cell-wall synthesis via oxygen-dependent pathways such as the catalase-peroxidase reaction. Isoniazid is bacteriostatic against resting bacilli and bactericidal against rapidly multiplying organisms, both extracellularly and intracellularly. The minimal inhibitory concentrations (MICs) of isoniazid for wild-type (untreated) strains of *M. tuberculosis* are <0.1 ug/mL, while those for *M. kansasii* are usually 0.5 to 2.0 ug/mL. The MICs of this drug for other mycobacteria are much higher.

*Pharmacology* Both oral and intramuscular preparations of isoniazid are readily absorbed. A 300-mg oral dose generally produces peak serum levels of 3 to 5 ug/mL. Isoniazid diffuses well throughout the body and reaches therapeutic concentrations in serum, cerebrospinal fluid (CSF), and infected tissue, including caseous granulomas. Isoniazid is metabolized in the liver via acetylation and hydrolysis; its metabolites are excreted into the urine. The rate of acetylation is genetically controlled. The recommended daily dose for the treatment of tuberculosis in the United States is 5 mg/kg for adults and 10 to 20 mg/kg for children, with a maximal daily dose of 300 mg for both groups. (Tuberculosis organizations outside the United States have recommended 5 mg/kg daily for both groups.) For intermittent therapy (usually directly observed), a maximal dose of 900 mg twice or thrice weekly is used. Even in moderate or severe renal failure, the adult dose rarely needs to be reduced below 200 mg/d.

*Adverse Effects (Table 168-3)* The two most important adverse effects of isoniazid

therapy are hepatotoxicity and peripheral neuropathy. Other adverse reactions are either rare or less significant and include rash (2%), fever (1.2%), anemia, acne, arthritic symptoms, a systemic lupus erythematosus-like syndrome, optic atrophy, seizures, and psychiatric symptoms. Isoniazid-associated hepatitis is idiosyncratic and increases in incidence with age. It occurs in 0.3% of treated persons under 35 years of age, 1.2% of those under 49 years of age, and 2.3% of those over 50 years of age. The risk of isoniazid-associated hepatitis is increased by daily alcohol consumption, concomitant rifampin administration, and slow isoniazid acetylation. Mortality rates from isoniazid-induced hepatitis have been reported to be 6 to 12%, but the real risk is certainly much lower: the reported rates were documented in high-risk patients who continued to take the drug despite progressive symptoms of hepatitis and without monitoring of liver enzyme levels. Liver enzymes are monitored in most settings among high-risk patients, and administration of the drug is discontinued at the onset of hepatitis. The American Thoracic Society (ATS) recommends that serum concentrations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) be determined at baseline in patients over 35 years of age who are receiving isoniazid for chemoprophylaxis, with monthly determinations thereafter. The benefit of such routine monitoring remains controversial, however. Measurement of the ALT or AST level is certainly mandatory whenever a patient notices the onset of symptoms suggestive of isoniazid-associated hepatitis (e.g., fever, anorexia, nausea, vomiting, and/or a flulike syndrome including fever and myalgias), and treatment should be discontinued until the relationship between therapy and symptoms is ascertained. Several studies have demonstrated that many patients with isoniazid intolerance can be desensitized. The ATS also recommends that discontinuation of isoniazid be strongly considered whenever an asymptomatic AST or ALT level exceeds 150 to 200 IU (three to five times the upper limit of normal) in high-risk patients whose baseline values were normal. In one study, only 11 (0.1%) of 11,141 patients had hepatotoxic reactions to isoniazid during preventive treatment.

Peripheral neuritis associated with isoniazid develops at a dose-dependent rate of 2 to 20% and probably relates to interference with pyridoxine (vitamin $B_6$) metabolism. This rate can be reduced to 0.2% with the prophylactic administration of 10 to 50 mg of pyridoxine daily.

*Resistance* Isoniazid-resistant mutants of *M. tuberculosis* occur spontaneously at a rate of 1 in $10^5$ to $10^6$organisms. The molecular sites of isoniazid resistance have been detailed. Almost all isoniazid-resistant strains have amino acid changes in the catalase-peroxidase gene (*katG*) or a two-gene locus known as *inhA*. Missense mutations or deletion of *katG* is also associated with reduced catalase and peroxidase activity. Primary isoniazid resistance is detected in 7% of untreated patients in native U.S. populations, but the percentage is much higher in many immigrant populations.

**Pyrazinamide** A derivative of nicotinic acid, pyrazinamide is an important bactericidal drug used in short-course therapy for tuberculosis.

*Pharmacology* Pyrazinamide is well absorbed after oral administration, with a plasma concentration range of 20 to 60 ug/mL 1 to 2 h after oral ingestion of 15 to 30 mg/kg, and is well distributed throughout the body. Levels in CSF are excellent, reaching 50 to 100% of levels in serum. The serum half-life of the drug is 9 to 11 h. Pyrazinamide is

metabolized by at least two major pathways and one minor pathway in the liver; its several metabolites include pyrazinoic acid, 5-hydroxypyrazinamide, and 5-hydroxypyrazinoic acid.

*Mechanism of Action* Pyrazinamide is similar to isoniazid in its narrow spectrum of antibacterial activity, which essentially includes only *M. tuberculosis*. The drug is bactericidal to slowly metabolizing organisms located within the acidic environment of the phagocyte or caseous granuloma; it is active only at a pH of<6.0. Pyrazinamide is considered a prodrug and is converted by the tubercle bacillus to the active form pyrazinoic acid. The target for this compound, however, remains unknown. Susceptible strains of *M. tuberculosis* are inhibited by 20 ug/mL.

*Adverse Effects (Table 168-3)* At the high dosages used in the past, hepatotoxicity was a prominent complication of pyrazinamide therapy. However, at the currently recommended daily dosage of 15 to 30 mg/kg, with a maximum of 2 g (which can be given in one dose), the frequency of hepatotoxicity is no higher than that for concomitant isoniazid and rifampin therapy. Although pyrazinamide is recommended by international tuberculosis organizations for routine use in pregnancy, it is not recommended in the United States because of inadequate teratogenicity data. Hyperuricemia is a common adverse effect of pyrazinamide therapy whose incidence is probably reduced by concurrent rifampin therapy. Clinical gout is seen only rarely. Polyarthralgias are encountered fairly commonly but are not related to hyperuricemia.

*Resistance* Resistance to pyrazinamide is associated with loss of pyrazinamidase activity such that pyrazinamide is no longer converted to pyrazinoic acid. More than 90% of isolates withMICs of>100 ug/mL have mutations in the *pncA* gene, which encodes for pyrazinamidase. All strains of *M. bovis* are naturally resistant to pyrazinamide and have a point mutation within the *pncA* gene.

## FIRST-LINE SUPPLEMENTAL DRUGS

**Ethambutol** A derivative of ethylenediamine, ethambutol is a water-soluble compound that is active only against mycobacteria. Susceptible species include *M. tuberculosis*, *M. marinum*, *M. kansasii*, and *M. avium-intracellulare* (MAI). Among first-line drugs, ethambutol is the least potent against *M. tuberculosis*. It is used most often with rifampin for the treatment of tuberculosis in patients who cannot tolerate isoniazid or who are thought or known to be infected with isoniazid-resistant organisms.

*Mechanism of Action* Ethambutol is bacteriostatic against rapidly growing mycobacteria. Its primary mechanism of action appears to be inhibition of arabinosyltransferases that mediate the polymerization of arabinose into arabinogalactan within the cell wall.

*Pharmacology* After oral administration, 75 to 80% of a dose of ethambutol is absorbed from the gastrointestinal tract. Serum levels peak at 2 to 4 ug/mL 2 to 4 h after a dose of 15 mg/kg. The drug's distribution throughout the body is adequate except in the CSF, where it reaches only low levels. However, ethambutol can reach CSF levels up to 50% as high as peak plasma levels when administered at a daily dose of 25 mg/kg to a patient with inflamed meninges. Almost all of the dose is excreted by the kidneys within 24 h of ingestion, either unchanged or as metabolites. The usual daily adult dosage of

ethambutol is 25 mg/kg (which may be given in one dose) for the first 2 months, with a subsequent reduction to 15 mg/kg. In cases where pretreatment is necessary, the higher dose may be given for the duration. For intermittent therapy, the dosage is 50 mg/kg twice weekly or 30 mg/kg three times weekly. The dosage must be lowered for patients with renal insufficiency (a creatinine clearance rate of <25 mL/min) to prevent drug accumulation and toxicity.

*Adverse Effects (Table 168-3)* Ethambutol is usually well tolerated. Retrobulbar optic neuritis is the most serious adverse effect; axial or central neuritis -- the only form reported in patients taking daily doses of <30 mg/kg -- involves the papillomacular bundle of fibers and results in reduced visual acuity, central scotoma, and loss of the ability to see green. Symptoms of ocular toxicity typically develop several months after the initiation of therapy, but rapid-onset optic neuritis has been reported. The risk of optic neuritis depends on the dose and duration of therapy: this reaction develops in 5% of patients receiving a daily dose of 25 mg/kg but in fewer than 1% of patients given a daily dose of 15 mg/kg. Patients taking the lower dose should be tested at baseline and whenever there is a subjective visual change for visual acuity and red-green color discrimination. Patients taking the higher dose should be tested at baseline, monthly thereafter, and whenever there is a subjective visual change. Optic neuritis with associated visual loss is usually reversible, but recovery may take 6 months or longer.

Other adverse effects of ethambutol are infrequent. Hyperuricemia occurs but is usually asymptomatic. Optic neuritis is rare at the low dose in children; however, the use of ethambutol in very young children is problematic because visual complications are difficult to monitor.

*Resistance* Resistance in *M. tuberculosis* relates to missense mutations in the *embB* gene that encodes for arabinosyltransferase. Such mutations have been found in 70% of resistant strains and involve amino acid residue 306 in approximately 90% of cases. Species of nontuberculous mycobacteria that are intrinsically resistant to ethambutol have variant amino acids in this region of the gene, while susceptible species have the same amino acid sequences as *M. tuberculosis*.

**Streptomycin** An aminoglycoside isolated from *Streptomyces griseus*, streptomycin is available for intramuscular and intravenous administration only. In the United States, it is the least-used first-line supplemental drug for tuberculosis because of its toxicity, the difficulty in obtaining adequateCSFlevels, and the inconvenience of its parenteral administration. In developing countries, however, streptomycin is frequently used because of its low cost. The drug is active against untreated strains of *M. tuberculosis*, *M. kansasii*, and *M. marinum* and against some strains ofMAI at readily achievable serum levels.

*Pharmacology* Serum levels of streptomycin peak at 25 to 40 ug/mL after a 1.0-g dose. Streptomycin is bactericidal for rapidly dividing extracellular mycobacteria but is ineffective in the acidic environment within the macrophage. It diffuses poorly into the meninges and, in patients with meningitis, reachesCSFlevels that are only 20% of serum levels.

The usual adult dose of streptomycin is 0.5 to 1.0 g (10 to 15 mg/kg) daily or five times

per week; the pediatric dose is 20 to 40 mg/kg daily, with a maximum of 1 g/d. Because streptomycin is eliminated almost exclusively by the kidneys, the dosage must be lowered and the frequency of administration reduced (to only two or three times per week) in most patients over 50 years of age and in any patient with renal impairment.

*Mechanism of Action* Streptomycin inhibits protein synthesis by disruption of ribosomal function.

*Adverse Effects (Table 168-3)* Adverse reactions to streptomycin therapy occur in 10 to 20% of patients. Ototoxicity and renal toxicity are the most common and the most serious. Renal toxicity, usually manifested as nonoliguric renal failure, is less common with streptomycin than with other frequently used aminoglycosides, such as gentamicin. Ototoxicity involves both hearing loss and vestibular dysfunction. The latter is more common and includes loss of balance, vertigo, and tinnitus. Patients receiving streptomycin must be monitored carefully for these adverse effects. Less serious reactions include perioral paresthesia, eosinophilia, rash, and drug fever.

*Resistance* Spontaneous resistance to streptomycin occurs in 1 in $10^5$ to $10^7$ organisms. In two-thirds of streptomycin-resistant strains of *M. tuberculosis*, mutations have been identified in one of two targets: a 16S rRNA gene (*rrs*) and the gene encoding ribosomal protein S12 (*rpsL*). Both targets are believed to be involved in streptomycin ribosomal binding. No mutational change has been identified in the other one-third of resistant isolates. Strains of *M. tuberculosis* that are resistant to streptomycin are not cross-resistant to capreomycin or amikacin.

## SECOND-LINE DRUGS

Second-line and/or newer antituberculous agents are used either when tuberculosis is drug resistant or when first-line supplemental drugs are not available. The most important second-line drugs are discussed below in the general (descending) order of usefulness.

**Capreomycin** Capreomycin, a complex cyclic polypeptide antibiotic derived from *Streptomyces capreolus*, is similar to streptomycin in terms of dosing, mechanism of action, pharmacology, and toxicity. It is administered only by the intramuscular route in doses of 10 to 15 mg/kg daily or five times per week (maximal daily dose, 1 g), with peak blood levels of 20 to 40 ug/mL. After 2 to 4 months, the dosage should be reduced to 1 g two or three times a week. Cross-resistance to kanamycin and amikacin -- but not to streptomycin -- is common. After streptomycin, capreomycin is the injectable drug of choice for tuberculosis.

**Amikacin and Kanamycin** These well-known aminoglycosides are bactericidal to extracellular organisms. Kanamycin is rarely used because of its toxicity. Amikacin is active against *M. tuberculosis* and several of the nontuberculous species, including the rapidly growing mycobacteria, *M. scrofulaceum*, *M. leprae*, and *MAI*. The usual adult dosage is 10 to 15 mg/kg intramuscularly or intravenously three to five times per week. Resistance to both drugs relates to a single-base-pair change at position 1408 in the 16S ribosomal RNA gene.

**Para-Aminosalicylic Acid** PAS, a calcium or sodium salt that inhibits the growth of *M. tuberculosis* by impairing folate synthesis, is rarely indicated for the treatment of tuberculosis because of its low level of antituberculous activity and its high level of gastrointestinal toxicity (manifesting as nausea, vomiting, and diarrhea). Enteric-coated PAS granules (4 g every 8 h) may be better tolerated than other formulations and produce higher therapeutic blood levels. PAS is well absorbed after oral administration but reaches only low concentrations in theCSF. The drug has a short half-life (1 h), and 80% of the dose is excreted in the urine.

**Thiacetazone** Also called amithiozone, thiacetazone is not available in the United States but -- because it is inexpensive and readily available -- is widely used in the developing world as a single-tablet combination with isoniazid to treat tuberculosis. The usual daily dosage is 150 mg. Thiacetazone is structurally related to isoniazid but is bacteriostatic and more toxic. The World Health Organization advises against the use of thiacetazone by HIV-infected patients because of an unacceptably high rate of severe adverse (gastrointestinal) and fatal (skin) reactions.

**Viomycin** A complex basic polypeptide antibiotic, viomycin has properties similar to those of capreomycin, amikacin, and kanamycin and must be administered by intramuscular injection. Ninety percent of strains of multidrug-resistant *M. tuberculosis* are inhibited by viomycin levels of 1 to 10 ug/mL. Toxic effects are more common and severe than with other polypeptide antibiotics. This drug is not available in the United States.

**Ethionamide** Like isoniazid and pyrazinamide, ethionamide is a derivative of isonicotinic acid. This agent is bacteriostatic against metabolizing *M. tuberculosis* and some nontuberculous mycobacteria. It is most useful in therapy for multidrug-resistant tuberculosis. However, its use is severely limited by its toxicity and frequent side effects, which include intense gastrointestinal intolerance (anorexia, vomiting, and dysgeusia), serious neurologic reactions, reversible hepatitis (5% of cases), hypersensitivity reactions, and hypothyroidism. Ethionamide is well absorbed orally and is widely distributed throughout the body at sites including theCSF.

**Cycloserine** Cycloserine (D-4-amino-3-isoxazolidinone) is produced by *Streptomyces orchidaceus* and is active against a broad spectrum of bacteria, including *M. tuberculosis*. Cycloserine is well absorbed after oral administration and is widely distributed throughout the body fluids, including theCSF. Serious side effects limit the use of this drug and include psychosis (with suicide in some cases), seizures, peripheral neuropathy, headaches, somnolence, and allergic reactions. Cycloserine should not be given to patients with epilepsy, active alcohol abuse, severe renal insufficiency, or a history of depression or psychosis.

**Newer Antituberculous Drugs** A number of other drugs are being evaluated for their antituberculous activity. This group includes rifabutin, rifapentine, the newer fluorinated quinolones, amoxicillin/clavulanic acid, clofazimine, clarithromycin, and rifamycins not yet approved by the U.S. Food and Drug Administration (FDA), such as KRM-1648 (benzoxazinorifamycin).

*Rifabutin* Rifabutin, a semisynthetic rifamycin spiropiperidyl derivative, shares many

characteristics with rifampin, including activity against *M. tuberculosis*. Rifabutin is also active against some strains of rifampin-resistant *M. tuberculosis* and is more active than rifampin againstMAI and other nontuberculous mycobacteria. To date, rifabutin has been most useful in the prophylaxis of disseminated MAI infection and in the treatment of drug-resistant tuberculosis. Because it seems to exhibit more antituberculous activity than rifampin in vitro and in animals, its possible clinical advantages over rifampin are being evaluated. In a multinational trial in which either rifampin (600 mg/d) or rifabutin (150 mg/d) was administered in combination with isoniazid plus a 2-month regimen of pyrazinamide and ethambutol, the two rifamycins were equally effective and well tolerated in the treatment of newly diagnosed pulmonary tuberculosis. Rifabutin is recommended in place of rifampin for the treatment of HIV-positive individuals who are also taking a protease inhibitor.

*PHARMACOLOGY* The pharmacology of rifabutin is dramatically different from that of rifampin. Rifabutin is readily absorbed after a single oral dose of 300 mg and reaches peak serum levels (0.35 ug/mL) in 2 to 4 h. This lipophilic drug distributes best to tissues: tissue levels are 5 to 10 times higher than plasma levels.CSFconcentrations are 30 to 70% of plasma levels in HIV-infected patients who have meningitis. The drug's slow clearance via hepatic metabolism and renal excretion results in a mean serum half-life of 45 h, which is much longer than the 3- to 5-h half-life of rifampin. Clarithromycin (but not azithromycin) and fluconazole appear to block the hepatic metabolism of rifabutin, with consequent increases in serum levels. When rifabutin is administered orally with food, its rate of absorption is slowed, but the extent of its absorption is unchanged. Adjustment of dosage is usually unnecessary in elderly patients and in patients with reduced hepatic or renal function.

*MECHANISM OF ACTION* In *Escherichia coli* and *Bacillus subtilis*, rifabutin inhibits DNA-dependent RNA polymerase in the same manner as rifampin. Its mode of action against mycobacteria is believed to be the same.

*ADVERSE EFFECTS* Most adverse effects of rifabutin are dose related and occur most frequently in patients receiving >300 mg/d. Discontinuation of therapy because of adverse drug reactions is reported in 16% of patients receiving rifabutin as opposed to 8% of those receiving a placebo. The most common symptoms are gastrointestinal; other reactions include rash, headache, asthenia, chest pain, myalgia, and insomnia. Like those taking rifampin, most patients taking rifabutin have discolored (orange to tan) urine and other body fluids. Less common adverse reactions include fever, chills, a flulike syndrome, hepatitis, *Clostridium difficile*-associated diarrhea, and a yellow skin discoloration ("pseudojaundice"). After a rifabutin dose of 450 to 600 mg in combination with clarithromycin, anterior uveitis is reported in up to 40% of patients; also common at these high doses are hyperpigmentation and the polymyalgia/arthralgia syndrome. All of these conditions are reversible when treatment is discontinued. Laboratory abnormalities include neutropenia, leukopenia, thrombocytopenia, and increased levels of liver enzymes.

Rifabutin induces the hepatic cytochrome P450 enzymes but does so much less strongly than rifampin. Drugs whose metabolism is enhanced by rifabutin include anticoagulants, quinidine, oral contraceptives, sulfonylureas, analgesics, dapsone, narcotics, glucocorticoids, clarithromycin, zidovudine, and cardiac glycosides.

*RESISTANCE* Resistance to rifabutin is attributable to the same mechanism as that to rifampin -- i.e., mutations involving the *rpoB* gene. However, of the 14 mutant *rpoB* alleles that confer resistance to rifampin, only nine confer high-level resistance to rifabutin, while the remaining five result in only small changes in rifabutinMICs, which remain £0.5 ug/mL. The MIC of rifabutin for susceptible strains of *M. tuberculosis* is low (<0.06 ug/mL), and the drug is considered clinically active against partially resistant strains that are inhibited by plasma levels of £0.5 ug/mL. Thus rifabutin inhibits about one-quarter of rifampin-resistant strains of *M. tuberculosis*.

*Rifapentine* A semisynthetic cyclopentyl rifamycin antibiotic, rifapentine has received accelerated approval from theFDA for the treatment of tuberculosis. It is the first new drug approved for tuberculosis in 25 years in the United States. While similar to rifampin, rifapentine is lipophilic and longer acting -- characteristics that enhance patient compliance; the drug can be administered at a dose of 600 mg once or twice weekly. It has antibacterial activity against *M. tuberculosis* but has undergone only minimal testing against nontuberculous mycobacteria. Rifapentine has not yet been approved for the treatment of patients with HIV disease because rifapentine/rifampin monoresistance frequently develops in HIV-positive patients receiving isoniazid plus rifapentine. Like rifampin, rifapentine is active against many nonmycobacterial organisms, including *Haemophilus influenzae*, *Bordetella pertussis*, *B. parapertussis*, *Brucella* spp., *Legionella* spp., *Neisseria* spp., streptococci, and staphylococci.

In a randomized comparative study, 672 Chinese patients received isoniazid plus either rifapentine or rifampin. The isoniazid/rifapentine group had a higher relapse rate (10% versus 5%) than the isoniazid/rifampin group. Nevertheless, this disadvantage was considered acceptable in light of the lower rate of adverse effects and less frequent administration in the isoniazid/rifapentine group.

*PHARMACOLOGY* Food enhances the oral absorption of rifapentine, while antacids impair its absorption. After oral administration with food, this drug reaches peak serum concentrations in 5 to 6 h and achieves a steady state in 10 days. The half-life of rifapentine and its active metabolite 25-desacetyl rifapentine is approximately 13 h. The drug is highly bound to serum protein (93 to 97%), and most of the administered dose is excreted via the liver (70%). Oral clearance is more rapid in males than in females (2.51 vs 1.69 L/h), but the clinical significance of this difference is unknown.

*MECHANISM OF ACTION* Rifapentine exerts its bactericidal effect by inhibiting DNA-dependent RNA polymerase in susceptible bacteria. TheMICs of rifapentine for rifampin-susceptible strains of *M. tuberculosis* range from 0.03 to 0.12 ug/mL.

*ADVERSE EFFECTS* Rifapentine demonstrates an adverse-event pattern similar to that of rifampin. Both drugs are frequently associated with hyperuricemia when administered with pyrazinamide and with elevated hepatocellular enzyme levels in 3 to 4% of patients when administered with other antituberculous agents. Liver enzyme levels should be monitored in patients receiving rifapentine who already have elevated liver enzyme concentrations or known liver disease. Like rifampin, rifapentine causes an orange-red discoloration of body fluids, including urine, saliva, and tears, and stains contact lenses.

Rifapentine induces the hepatic cytochrome P450 enzymes CYP3A4 and 2C8/9. Current induction studies suggest that its potential for drug-drug interaction may be less than that of rifampin but greater than that of rifabutin. Other drugs potentially affected by concomitant administration of rifapentine are listed inTable 168-2.

Rifapentine is in category C for use in pregnancy (Table 168-1) because of its teratogenesis in rats and rabbits. There are insufficient data concerning use of this drug in pregnant and breast-feeding patients.

*RESISTANCE* Strains of *M. tuberculosis* resistant to rifapentine, rifampin, and rifabutin all involve spontaneous point mutations in the *rpoB* gene. All strains resistant to rifampin are also resistant to rifapentine.

*Quinolones* A surprisingly large number of fluorinated quinolones are being developed and studied as inhibitors of mycobacteria. Their mode of action presumably is the prevention of DNA synthesis through the inhibition of DNA gyrase. Ofloxacin, ciprofloxacin, sparfloxacin, and pefloxacin are active against many mycobacteria, including *M. tuberculosis*, *M. leprae*, *M. marinum*, *M. kansasii*, and *M. fortuitum*. These drugs are well absorbed orally, reach high serum levels, and distribute well to body tissues and fluids. While not approved for antituberculous therapy in the United States, ofloxacin -- used in combination with isoniazid and rifampin for the treatment of pulmonary tuberculosis -- has been as active and safe as ethambutol in initial trials. Adverse effects are relatively uncommon, occurring in 0.5 to 10% of cases and consisting mostly of benign reactions such as gastrointestinal intolerance, rashes, dizziness, and headache. However, more serious adverse effects are being reported and include confusion, seizures, interstitial nephritis, skin vasculitis, and acute renal failure.

Mycobacterial resistance to the fluoroquinolones develops rapidly. Its molecular basis is complex; only some strains exhibit missense mutations in the A subunit (*gyrA* gene) of DNA gyrase. Fluoroquinolone-resistant tuberculosis is a source of growing concern: 22 such cases were reported recently from New York City. Antituberculous therapy with quinolones should be reserved for patients with multidrug resistance or those who cannot tolerate first-line drugs.

## LEPROSY (HANSEN'S DISEASE)

Therapy for leprosy remains difficult, especially in developing countries, because of the long course required, the high cost and low availability of most drugs, the frequency of adverse reactions to drugs, the acquisition of drug resistance, the difficulty of determining a disease end point or cure, and (given that *M. leprae* still cannot be grown in vitro) the difficulty of conducting susceptibility testing. While many drugs are active against *M. leprae*, efficacy in the treatment of leprosy has been established only for dapsone, rifampin, clofazimine, and ethionamide.

**Rifampin** Rifampin is considered the most active agent for the treatment of leprosy. Its worldwide use is limited only by its cost. This drug is markedly bactericidal against *M. leprae* and reduces the number of viable bacilli in the patient's tissues faster than any other available agent. Rifampin must be combined with other antileprosy drugs to

forestall resistance. For cost reasons, the drug is given at a dose of 600 mg once a month (supervised) outside the United States, but it is given daily in the United States. For details on pharmacology, adverse events, and resistance, see relevant sections under "Tuberculosis."

**Dapsone** Dapsone (4,4¢-diaminodiphenylsulfone) inhibits bacterial folic acid synthesis. It is now considered the second drug of choice (after rifampin) in most cases of Hansen's disease because of its ready availability, low cost, and low toxicity and the susceptibility of untreated strains of *M. leprae* to very low concentrations.

*Pharmacology* Dapsone is well absorbed orally and distributes well throughout the body. The usual daily dosage is 100 mg for adults and 0.9 to 1.4 mg/kg for children. Plasma concentrations peak within 1 to 3 h. The median elimination half-life is 22 h. Dapsone is cleared by acetylation in the liver, with genetic variation similar to that documented for the acetylation of isoniazid. The drug is 70% bound to plasma protein. Usual daily doses produce serum concentrations of 10 to 15 ug/mL, which far exceed theMIC for *M. leprae* (0.01 to 0.001 ug/mL).

*Adverse Effects* Hemolysis and methemoglobinemia are common untoward reactions to dapsone. Patients should be screened for glucose-6-phosphate dehydrogenase deficiency to prevent drug-induced hemolysis. However, most patients tolerate dapsone therapy well with adequate clinical and laboratory supervision. Other side effects include gastrointestinal intolerance, headache, pruritus, peripheral neuropathies, nephritic syndrome, fever, and rash. In lepromatous and borderline lepromatous leprosy, erythema nodosum leprosum (ENL) may occur. This reaction may be difficult to distinguish from reactions of leprosy, including drug reactions and the infectious mononucleosis-like dapsone syndrome.

**Clofazimine** A phenazine iminoquinone dye, clofazimine is weakly bactericidal against *M. leprae*. It is useful in treating dapsone-resistant leprosy and may lessen the severity of ENL. Clofazimine's mode of action is not well understood, but the drug may inhibit DNA binding. It is absorbed orally and distributed to the fatty tissues and the reticuloendothelial system. Its serum half-life is about 60 to 70 days; only a small proportion of the dose is excreted daily into the urine or bile. Bactericidal activity is very slow and is evident for about 50 days after administration. The usual adult dosage is 50 to 100 mg/d, 100 mg three times a week, or (for treatment of ENL) 300 mg/d. Untoward effects include skin discoloration and, less commonly, gastrointestinal intolerance. Clofazimine was reported to be responsible for a case of cardiotoxicity induced via ventricular arrhythmia. Even though clofazimine-resistant disease has been reported only rarely when this agent is used alone, it should be used with other effective antibiotics. Clofazimine is active in vitro against some nontuberculous mycobacterial species, includingMAI, *M. kansasii*, *M. simiae*, and *M. abscessus*.

**Ethionamide** While ethionamide (250 mg/d) has not been approved by theFDA for the treatment of leprosy, it is sometimes used in the United States in combination with rifampin (600 mg/d) to treat dapsone-resistant leprosy in patients who cannot accept the skin-depigmentation effect of clofazimine. Because resistance to ethionamide develops quickly when the drug is used alone, it must be used with other effective agents. Patients should be monitored closely for hepatotoxicity when taking ethionamide

(especially in combination with rifampin), and treatment should be discontinued if the patient'sALTlevels exceed 2.5 times the normal value. Prothionamide, a congener of ethionamide that is not available in the United States, has pharmacologic properties similar to those of ethionamide and is widely used throughout the world.

**Other Agents** A number of other drugs exhibit significant activity against *M. leprae*, but clinical experience with these agents is lacking. Thalidomide is now approved by theFDA for treatment ofENL. Although this drug may be useful in suppressing ENL, it acts as a tranquilizer, is extremely teratogenic, and should *never* be taken by anyone who is or may become pregnant. Physicians wishing to prescribe thalidomide must register with the System for Thalidomide Education and Prescription Safety (S.T.E.P.S.) at 1-888-423-5436 (Celgese Corporation).

The newer macrolide antibiotics (particularly clarithromycin), minocycline (a long-acting tetracycline), and a number of fluoroquinolones (including ofloxacin, sparfloxacin, and pefloxacin) have shown promising bactericidal activity against *M. leprae*. Ofloxacin and minocycline are being investigated with rifampin in short-course regimens for lepromatous disease. All of these newer leprosy drugs have low toxicity profiles, modes of action different from those of the established agents, and powerful bactericidal activity against *M. leprae*. However, their levels of bactericidal activity are lower than that of rifampin.

## NONTUBERCULOUS MYCOBACTERIA

Although less pathogenic than *M. tuberculosis*, the nontuberculous mycobacteria can cause pulmonary, skin, bone and joint, lymph node, and soft tissue infection as well as disseminated disease in immunocompromised hosts, including patients with AIDS.MAI and *M. kansasii* are the two most common causes of nontuberculous mycobacterial pulmonary infection. Up to 40% of AIDS patients develop disseminated disease due to MAI.

**Clarithromycin** Clarithromycin (6-*O*-methylerythromycin) is a new macrolide that is similar to erythromycin in its mechanism of action. However, unlike erythromycin, it is well absorbed with or without meals and elicits little gastrointestinal intolerance at low doses. Clarithromycin distributes well into body tissues and fluids and is highly concentrated in macrophages. The drug is metabolized in the liver, and approximately 30% of a given dose is excreted in the urine. The dosage should be reduced if the creatinine clearance rate is£30 mL/min. Like erythromycin, clarithromycin binds with plasma proteins (65 to 70%) and can raise the levels of drugs such as theophylline and carbamazepine. As noted earlier, serum levels of clarithromycin are reduced by the concomitant administration of rifampin and to a lesser degree by that of rifabutin; clarithromycin treatment increases serum levels of rifabutin and some antihistamines (e.g., terfenadine), thus increasing their toxicity. Clarithromycin and (probably) azithromycin are the most active agents for the treatment ofMAIinfections; one of these drugs is considered an essential component of any regimens for this purpose. However, because of mutational drug resistance, clarithromycin should be given in combination with other agents, such as ethambutol and rifampin or rifabutin. The drug is also highly active against almost all other nontuberculous mycobacteria, including *M. marinum*, *M. kansasii*, *M. haemophilum*, *M. genavense*, *M. xenopi*, *M. abscessus*, *M. chelonae*, and

most isolates of *M. fortuitum*. Standard antimycobacterial doses have been 500 mg twice daily; doses of 1000 mg twice daily have been associated with increased mortality among patients with AIDS and disseminated MAI disease. The more common side effects of high doses include nausea, vomiting, a bitter taste, and (occasionally) abnormal liver-function tests. Most side effects can be minimized by reducing the dose, usually by 50%. Clarithromycin is teratogenic in laboratory animals and is in category C for use in pregnancy (Table 168-1). Mutational resistance occurs in one in $10^8$ to $10^9$organisms and develops rapidly with monotherapy, especially that for disseminated MAI disease. Resistance results from point mutations involving adenine at positions 2058 or 2059 in the 23S ribosomal binding site.

**Azithromycin** Azithromycin is a macrolide that belongs to the family of azalides. It reaches much lower serum levels than clarithromycin (usually £0.5 ug/mL) but attains high tissue and macrophage concentrations and has a longer half-life, which suggests the feasibility of intermittent therapy. It is involved in few drug interactions since it does not affect the cytochrome P450 system. The usual dose is 250 to 500 mg/d. No alteration in dose is required in renal failure. The most common side effects are gastrointestinal symptoms and reversible hearing loss. Azithromycin appears to be less active than clarithromycin for both pulmonary and disseminatedMAIdisease. Resistance to azithromycin develops by the same mechanism as that to clarithromycin, with cross-resistance between the two macrolides.

## THERAPY FOR SPECIFIC NONTUBERCULOUS MYCOBACTERIA

**MAI** First-line antituberculous drugs are much less active against MAI than against *M. tuberculosis*. Therapy for MAI is controversial because of the lack of controlled clinical trials. In 1990 theATSrecommended the following four-drug regimen for MAI lung disease in HIV-negative patients: 18 to 24 months of isoniazid (300 mg), rifampin (600 mg), and ethambutol (25 mg/kg, then 15 mg/kg beginning in the third month), with intermittent streptomycin. However, two subsequent events -- the demonstration of the dramatic activity of clarithromycin against both pulmonary and disseminated MAI infection and the introduction of rifabutin -- have altered the therapeutic approach to MAI infection. In the 1997 ATS recommendations for MAI lung disease, clarithromycin (500 mg twice daily) now replaces isoniazid, and rifabutin (300 mg/d) is often used in place of rifampin. Therapy for pulmonary disease is generally given until cultures have been negative for 12 months.

For disseminated disease in AIDS, one of the newer macrolides (clarithromycin or azithromycin) and ethambutol (15 mg/kg) are considered essential components of any treatment regimen, with rifabutin (300 mg) a commonly used third drug in patients not taking a protease inhibitor for their HIV infection. Other alternative drugs include ciprofloxacin, streptomycin, and amikacin. Clofazimine appears to increase mortality and should be avoided. For the prophylaxis of disseminatedMAIdisease, rifabutin (300 mg/d), clarithromycin (500 mg twice daily), and azithromycin (1200 mg once weekly) have all been demonstrated to be effective in controlled or comparative clinical trials.

***Mycobacterium kansasii*** *M. kansasii* is usually susceptible to most antituberculous drugs except for pyrazinamide. CurrentATSrecommendations for the treatment of *M. kansasii* pulmonary disease are 18 to 24 months of daily isoniazid (300 mg), rifampin

(600 mg), and ethambutol (15 mg/kg). In patients taking protease inhibitors, rifabutin (150 mg) or clarithromycin (500 mg) twice daily should be substituted for rifampin. The potential advantages of the highly active rifabutin and the newer macrolides in immunocompetent patients have not been studied.

**Rapidly Growing Mycobacteria** *M. fortuitum*, *M. abscessus*, and *M. chelonae* account for more than 80% of cases of clinical disease due to rapidly growing mycobacteria. These organisms are resistant to antituberculous agents other than amikacin but are variably susceptible to several other antibiotics. Clarithromycin has dramatically changed the approach to therapy for infection with these organisms, as it inhibits all rapidly growing mycobacteria -- except for 20% of *M. fortuitum* strains and most *M. smegmatis* strains -- at concentrations of£4 ug/mL. Other drugs with good activity include amikacin (which inhibits 80 to 100% of strains), cefoxitin (80% of *M. abscessus* and *M. fortuitum* strains), doxycycline (50% of *M. fortuitum* strains), imipenem (100% of *M. fortuitum* strains, 70% of *M. chelonae* strains, and 70% of *M. abscessus* strains), the fluorinated quinolones ciprofloxacin and ofloxacin (100% of *M. fortuitum* strains), and sulfonamides (90% of *M. fortuitum* strains).

***Mycobacterium marinum*** *M. marinum*, a photochromogen, is typically susceptible to minocycline, rifampin, ethambutol, clarithromycin, and trimethoprim-sulfamethoxazole and is resistant to isoniazid.

***Mycobacterium haemophilum*** Infection due to *M. haemophilum* occurs most commonly as disseminated disease in immunocompromised patients with or without AIDS. This organism can cause bone and joint infection and skin infection. Isolates typically show in vitro resistance to most drugs but may be susceptible to rifampin, rifabutin, quinolones, and clarithromycin.

***Mycobacterium xenopi*** In the United States, *M. xenopi* most often causes nosocomial infections; these infections most commonly occur in the environment of the hospital's hot-water system. In one study from Brooklyn, NY, *M. xenopi* was the second most common pathogenic nontuberculous mycobacterial species; of the 86 hospitalized patients from whom it was isolated, 41% were HIV-positive. Drug therapy for *M. xenopi* infection is difficult because in vitro drug sensitivity tests do not reliably predict clinical results. *M. xenopi* is often resistant to first-line antituberculous agents but susceptible to the newer macrolides, quinolones, streptomycin, and ethionamide.

***Mycobacterium genavense*** *M. genavense* is a newly recognized organism that grows only in liquid media, such as Bactec 12B or 13A. This organism almost exclusively infects AIDS patients, causing disseminated disease and being isolated from blood, bone marrow, liver, lymph node, spleen, and intestinal cultures. The in vitro susceptibility profile of *M. genavense* has not been well established. Some isolates are susceptible to amikacin, clarithromycin, ofloxacin, rifampin, and rifabutin.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 169. TUBERCULOSIS - *Mario C. Raviglione*, *Richard J. O'Brien*

### DEFINITION

Tuberculosis, one of the oldest diseases known to affect humans, is caused by bacteria belonging to the *Mycobacterium tuberculosis* complex. The disease usually affects the lungs, although in up to one-third of cases other organs are involved. If properly treated, tuberculosis caused by drug-susceptible strains is curable in virtually all cases. If untreated, the disease may be fatal within 5 years in more than half of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary tuberculosis.

### ETIOLOGIC AGENT

Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the *M. tuberculosis* complex, the most frequent and important agent of human disease is *M. tuberculosis* itself. The complex includes *M. bovis* (the bovine tubercle bacillus, once an important cause of tuberculosis transmitted by unpasteurized milk and currently the cause of a small percentage of cases in developing countries), *M. africanum* (isolated in a small proportion of cases in West and Central Africa), and *M. microti* (the "vole" bacillus, a closely related but rarely encountered organism).

*M. tuberculosis* is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring about 0.5 um by 3 um. Mycobacteria, including *M. tuberculosis*, do not stain readily and are often neutral on Gram's staining. However, once stained, the bacilli cannot be decolorized by acid alcohol, a characteristic justifying their classification as acid-fast bacilli (AFB). Acid fastness is due mainly to the organisms' high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Microorganisms other than mycobacteria that display some acid fastness include species of *Nocardia* and *Rhodococcus*, *Legionella micdadei*, and the protozoa *Isospora* and *Cryptosporidium*. In the mycobacterial cell wall, lipids (e.g., mycolic acids) are linked to underlying arabinogalactan and peptidoglycan. This structure is responsible for the very low permeability of the cell wall and thus for the ineffectiveness of most antibiotics against the organism. Another molecule in the mycobacterial cell wall, lipoarabinomannan, is involved in the pathogen-host interaction and facilitates the survival of *M. tuberculosis* within macrophages. The several proteins characteristic of *M. tuberculosis* include those in purified protein derivative (PPD) tuberculin, a precipitate of non-species-specific molecules obtained from filtrates of heat-sterilized, concentrated broth cultures. The complete genome sequence of *M. tuberculosis* comprises about 4000 genes and has a high guanine-plus-cytosine content. A large proportion of the genes are devoted to the production of enzymes involved in lipogenesis and lipolysis and of glycine-rich proteins that are probably responsible for antigenic variations.

### EPIDEMIOLOGY

Between 3.5 and 4 million new cases of tuberculosis -- all forms (pulmonary and extrapulmonary), 90% of them from developing countries -- were reported annually to the World Health Organization (WHO) in the late 1990s. However, because of a low

level of case detection and incomplete notifications in many national programs, reported cases represent only a fraction of the total. It is estimated that 8 million new cases of tuberculosis occurred worldwide in 1997, 95% of them in developing countries of Asia (5 million), Africa (1.6 million), the Middle East (0.6 million), and Latin America (0.4 million). It is also estimated that nearly 2 million deaths from tuberculosis occurred in 1997, 98% of them in developing countries.

Beginning in the mid-1980s in many industrialized countries, the number of tuberculosis case notifications, which had been falling steadily, stabilized or even began to increase. This phenomenon was first noted in the United States but was soon observed in many European countries as well. A number of factors were implicated in the resurgence of tuberculosis in the United States in 1986 through 1992 -- most notably, immigration from countries with a high prevalence of tuberculosis; infection with HIV; emergence of multidrug-resistant (MDR) tuberculosis due to strains resistant at least to isoniazid and rifampin; and social problems such as poverty, homelessness, and drug abuse. In some areas (e.g., New York City), deterioration in the public health system and dismantling of tuberculosis management services also contributed to the worsening situation.With the implementation of stronger control programs, cases began to decrease in 1993. In 1998, 18,361 cases of tuberculosis (6.8 per 100,000 population) were reported to the U.S. Centers for Disease Control and Prevention (CDC) -- a 31% decrease from the 1992 peak.

In the United States, tuberculosis is uncommon among young adults of European descent, who have only rarely been exposed to *M. tuberculosis* infection during recent decades. In contrast, because of a high risk in the past, the prevalence of *M. tuberculosis* infection is relatively high among elderly Caucasians, who remain at increased risk of developing active tuberculosis. Tuberculosis in the United States is also a disease of young adult members of the HIV-infected, immigrant, and disadvantaged/marginalized populations. Similarly, in Europe, tuberculosis has reemerged as an important public health problem, mainly as a result of cases among immigrants from high-prevalence countries.

In developing countries of Africa and Asia, tuberculosis trends over the past several decades are not entirely clear. However, in sub-Saharan African countries with reliable reporting systems, the recent spread of the HIV epidemic has been accompanied by doubling or tripling of the number of reported cases of tuberculosis during a period as short as 10 years. The growing number of young adults with *M. tuberculosis* infection has fueled the rates of active tuberculosis in many developing countries. Without greater control efforts, the annual incident cases of tuberculosis globally may increase by 40% between now and 2020.

**From Exposure to Infection** *M. tuberculosis* is most commonly transmitted from a patient with infectious pulmonary tuberculosis to other persons by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5 to 10 um in diameter) may remain suspended in the air for several hours and may gain direct access to the terminal air passages when inhaled. There may be as many as 3000 infectious nuclei per cough. In the past, a frequent source of infection was raw milk containing *M. bovis* from tuberculous cows. Other routes of transmission of tubercle bacilli, such as through the skin or the placenta, are uncommon and of no

epidemiologic significance.

The probability of contact with a case of tuberculosis, the intimacy and duration of that contact, the degree of infectiousness of the case, and the shared environment of the contact are all important determinants of transmission. Several studies of close contacts have clearly demonstrated that tuberculosis patients whose sputum containsAFBvisible by microscopy play the greatest role in the spread of infection. These patients often have cavitary pulmonary disease or tuberculosis of the respiratory tract (endobronchial or laryngeal tuberculosis) and produce sputa containing as many as $10^5$AFB/mL. Patients with sputum smear-negative/culture-positive tuberculosis are less infectious, and those with culture-negative pulmonary disease and extrapulmonary tuberculosis are essentially noninfectious. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli, since it increases the intensity of contact with a case.

In short, the risk of acquiring *M. tuberculosis* infection is determined mainly by exogenous factors. Because of delays in seeking care and in diagnosis, it is estimated that up to 20 contacts will usually be infected by eachAFB-positive case before detection in high-prevalence countries.

**From Infection to Disease** Unlike the risk of acquiring infection with *M. tuberculosis*, the risk of developing disease after being infected depends largely on endogenous factors, such as the individual's innate susceptibility to disease and level of function of cell-mediated immunity. Clinical illness directly following infection is classified as *primary tuberculosis* and is common among children up to 4 years of age. Although this form may be severe and disseminated, it is usually not transmissible. When infection is acquired later in life, the chance is greater that the immune system will contain it, at least temporarily. The majority of infected individuals who ultimately develop tuberculosis do so within the first year or two after infection. Dormant bacilli, however, may persist for years before being reactivated to produce *secondary* (or *postprimary*) *tuberculosis*, which is often infectious. Overall, it is estimated that about 10% of infected persons will eventually develop active tuberculosis. *Reinfection* of a previously infected individual, which is probably common in areas with high rates of tuberculosis transmission, may also favor the development of disease. Molecular typing and comparison of strains of *M. tuberculosis* have suggested that up to one-third of cases of active tuberculosis in U.S. inner-city communities are due to recent transmission rather than to reactivation of latent infection.

Age is an important determinant of the risk of disease after infection. Among infected persons, the incidence of tuberculosis is highest during late adolescence and early adulthood; the reasons are unclear. The incidence among women peaks at 25 to 34 years of age. In this age group rates among women are usually higher than those among men, while at older ages the opposite is true. The risk may increase in the elderly, possibly because of waning immunity and comorbidity.

A variety of diseases favor the development of active tuberculosis. The most potent risk factor for tuberculosis among infected individuals is clearly HIV co-infection, which suppresses cellular immunity. The risk that latent *M. tuberculosis* infection will proceed to active disease is directly related to the patient's degree of immunosuppression. In a

study of HIV-infected, PPD-positive persons, this risk varied from 2.6 to 13.3 cases per 100 person-years and depended upon the CD4+ cell count. The risk of developing tuberculosis is significantly greater among HIV-infected than among HIV-uninfected hosts. Other conditions known to increase the risk of active tuberculosis among persons infected with tubercle bacilli include silicosis; lymphoma, leukemia, and other malignant neoplasms; hemophilia; chronic renal failure and hemodialysis; insulin-dependent diabetes mellitus; immunosuppressive treatment, including that administered for solid-organ transplantation; and conditions associated with malnutrition, such as gastrectomy and jejunoileal bypass surgery. Finally, the presence of old, self-healed, fibrotic tuberculous lesions constitutes a serious risk of active disease.

## NATURAL HISTORY OF DISEASE

Studies conducted in various countries before the advent of chemotherapy clearly showed that untreated tuberculosis is often fatal. About one-third of patients died within 1 year after diagnosis, and one-half within 5 years. Five-year mortality among sputum smear-positive cases was 65%. Of the survivors at 5 years, about 60% had undergone spontaneous remission, while the remainder were still excreting tubercle bacilli.

The introduction of effective chemotherapy has markedly affected the natural history of tuberculosis. With proper treatment, patients have a high chance of being cured. However, improper use of antituberculosis drugs, while reducing mortality, may also result in large numbers of chronic infectious cases, often with drug-resistant bacilli.

## PATHOGENESIS AND IMMUNITY

The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing microorganisms from infectious patients are inhaled. While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually fewer than 10%) reach the alveoli. There, nonspecifically activated alveolar macrophages ingest the bacilli. Invasion of macrophages by mycobacteria may result in part from association of C2a with the bacterial cell wall followed by C3b opsonization of the bacteria and recognition by the macrophages. The balance between the bactericidal activity of the macrophage and the virulence of the bacillus (the latter being partially linked to the bacterium's lipid-rich cell wall and to its glycolipid capsule, both of which confer resistance to complement and free radicals of the phagocyte) determines the events following phagocytosis. The number of invading bacilli is also important.

Several genes thought to confer virulence to *M. tuberculosis* have been identified. *katG* encodes for catalase, an enzyme protective against oxidative stress; *rpoV* is the main sigma factor initiating transcription of several genes. Defects in these two genes result in loss of virulence. The *erp* gene, encoding a protein required for multiplication, also contributes to virulence. The effects of a highly virulent strain are exemplified by an outbreak of tuberculosis in two rural counties in Tennessee and Kentucky in 1994 through 1996. In this outbreak, both epidemiologic evidence of enhanced transmission with high rates of disease and accelerated growth of the strain in mice were documented.

Several observations suggest that genetic factors play a key role in innate nonimmune resistance to infection with *M. tuberculosis*. The existence of this resistance is suggested by the differing degrees of susceptibility to tuberculosis in different populations. In mice, a gene called *Nramp1* (natural resistance-associated macrophage protein 1) has a regulatory role in resistance/susceptibility to mycobacteria. The human homologue NRAMP1, cloned to chromosome 2q, may have a role in determining susceptibility to tuberculosis. In a study among West Africans, subjects heterozygous for two polymorphisms of NRAMP1 (INT4 and 3¢UTR) had an apparently increased risk of tuberculosis, a finding suggesting that the susceptibility allele behaves as dominant.

In the initial stage of host-bacterium interaction, either the host's macrophages contain bacillary multiplication by producing proteolytic enzymes and cytokines or the bacilli begin to multiply. If the bacilli multiply, their growth quickly kills the macrophages, which lyse. Nonactivated monocytes attracted from the bloodstream to the site by various chemotactic factors ingest the bacilli released from the lysed macrophages. These initial stages of infection are usually asymptomatic.

About 2 to 4 weeks after infection, two additional host responses to *M. tuberculosis* develop: a tissue-damaging response and a macrophage-activating response. The *tissue-damaging response* is the result of a delayed-type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys nonactivated macrophages that contain multiplying bacilli. The *macrophage-activating response* is a cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the form of tuberculosis that will develop subsequently.

With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion, granulomatous lesions (tubercles) are formed. These lesions consist of lymphocytes and activated macrophages, such as epithelioid cells and giant cells. Initially, the newly developed tissue-damaging response is the only event capable of limiting mycobacterial growth within macrophages. This response, mediated by various bacterial products, not only destroys macrophages but also produces early solid necrosis in the center of the tubercle. Although *M. tuberculosis* can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis and calcification, while others undergo further evolution.

Cell-mediated immunity is critical at this early stage. In the majority of infected individuals, local macrophages are activated when bacillary antigens processed by macrophages stimulate T lymphocytes to release a variety of lymphokines. These activated cells aggregate around the lesion's center and effectively neutralize tubercle bacilli without causing further tissue destruction. In the central part of the lesion, the necrotic material resembles soft cheese (*caseous necrosis*). Even when healing takes place, viable bacilli may remain dormant within macrophages or in the necrotic material for years or even throughout the patient's lifetime. These "healed" lesions in the lung parenchyma and hilar lymph nodes may later undergo calcification (*Ranke complex*).

In a minority of cases, the macrophage-activating response is weak, and mycobacterial

growth can be inhibited only by intensifiedDTHreactions, which lead to tissue destruction. The lesion tends to enlarge further, and the surrounding tissue is progressively damaged. At the center of the lesion, the caseous material liquefies. Bronchial walls as well as blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing large numbers of bacilli, is drained through bronchi. Within the cavity, tubercle bacilli multiply well and spread into the airways and the environment through expectorated sputum.

In the early stages of infection, bacilli are usually transported by macrophages to regional lymph nodes, from which they disseminate widely to many organs and tissues. The resulting lesions may undergo the same evolution as those in the lungs, although most tend to heal. In young children with poor natural immunity, hematogenous dissemination may result in fatal miliary tuberculosis or tuberculous meningitis.

Cell-mediated immunity confers partial protection against *M. tuberculosis*, while humoral immunity has no defined role in protection. Two types of cells are essential: macrophages, which directly phagocytize tubercle bacilli, and T cells (mainly CD4+ lymphocytes), which induce protection through the production of lymphokines.

After infection with *M. tuberculosis*, alveolar macrophages secrete a number of cytokines: interleukin (IL) 1 contributes to fever; IL-6 contributes to hyperglobulinemia; and tumor necrosis factor a(TNF-a) contributes to the killing of mycobacteria, the formation of granulomas, and a number of systemic effects, such as fever and weight loss. Macrophages are also critical in processing and presenting antigens to T lymphocytes; the result is a proliferation of CD4+ lymphocytes, which are crucial to the host's defense against M*. tuberculosis*. Qualitative and quantitative defects of CD4+ T cells explain the inability of HIV-infected individuals to contain mycobacterial proliferation. Reactive CD4+ lymphocytes produce cytokines of the $T_H1$ pattern and participate in MHC class II-restricted killing of cells infected with *M. tuberculosis*. $T_H1$ CD4+ cells produce interferon g(IFN-g) and IL-2 and promote cell-mediated immunity. $T_H2$ cells produce IL-4, IL-5, and IL-10 and promote humoral immunity. The interplay of these various cytokines and their cross-regulation determine the host's response. The role of cytokines in promoting intracellular killing of mycobacteria has not been entirely elucidated. IFN-gmay induce release of nitric oxide, and TNF-a seems also to be important. Finally, the role of other cells, such as natural killer (NK) cells, "double-negative" CD4-CD8- cells, andg/d T cells, in protective immunity remains unclear.

*M. tuberculosis* possesses various protein antigens. Some are present in the cytoplasm and cell wall; others are secreted. That the latter are more important in eliciting a T lymphocyte response is suggested by experiments documenting the appearance of protective immunity in animals after immunization with live, protein-secreting mycobacteria. Among the antigens with a potential protective role are the 30-kDa (or 85B) and the ESAT-6 antigens. Protective immunity is probably the result of reactivity to a large number of different mycobacterial antigens.

Coincident with the appearance of immunity,DTH to *M. tuberculosis* develops. This reactivity is the basis of thePPD skin test, currently the only test that reliably detects *M. tuberculosis* infection in persons without symptoms. The cellular mechanisms

responsible for PPD reactivity are related mainly to previously sensitized CD4+ lymphocytes, which are attracted to the skin-test site. There, they proliferate and produce cytokines.

In 1891, Robert Koch discovered components of *M. tuberculosis* in a concentrated liquid culture medium. Subsequently named "old tuberculin" (OT), this material was initially believed to be useful in the treatment of tuberculosis (although this idea was later disproved). It soon became clear that OT was capable of eliciting a skin reaction when injected subcutaneously into patients with tuberculosis. In 1932, Seibert and Munday purified this product by ammonium sulfate precipitation. The result was an active protein fraction known as tuberculinPPD. However, the complexity and diversity of the constituents of PPD rendered its standardization difficult. PPD-S, developed by Seibert and Glenn in 1941, was chosen as the international standard. Later, theWHO and UNICEF sponsored large-scale production of a master batch of PPD, termed RT23, and made it available for general use. The greatest limitation of PPD is its lack of mycobacterial species specificity, a property that is due to the large number of proteins in this product that are highly conserved in the various species of mycobacteria.

WhileDTH is associated with protective immunity (PPD-positive persons being less susceptible to a new *M. tuberculosis* infection than PPD-negative persons), it by no means guarantees protection against reactivation. In fact, severe cases of active tuberculosis are often accompanied by strongly positive skin-test reactions.

## CLINICAL MANIFESTATIONS

Tuberculosis is usually classified as pulmonary or extrapulmonary. Before the recognition of HIV infection, more than 80% of all cases of tuberculosis were limited to the lungs. However, up to two-thirds of HIV-infected patients with tuberculosis may have both pulmonary and extrapulmonary disease or extrapulmonary disease alone.

**Pulmonary Tuberculosis** Pulmonary tuberculosis can be categorized as primary or postprimary (secondary).

*Primary Disease* Primary pulmonary tuberculosis results from an initial infection with tubercle bacilli. In areas of high tuberculosis prevalence, this form of disease is often seen in children and is frequently localized to the middle and lower lung zones. The lesion forming after infection is usually peripheral and accompanied by hilar or paratracheal lymphadenopathy, which may not be detectable on chest radiography. In the majority of cases, the lesion heals spontaneously and may later be evident as a small calcified nodule (*Ghon lesion*).

In children and in persons with impaired immunity, such as those with malnutrition or HIV infection, primary pulmonary tuberculosis may progress rapidly to clinical illness. The initial lesion increases in size and can evolve in different ways. Pleural effusion, a frequent finding, results from the penetration of bacilli into the pleural space from an adjacent subpleural focus. In severe cases, the primary site rapidly enlarges, its central portion undergoes necrosis, and acute cavitation develops (progressive primary tuberculosis). Tuberculosis in young children is almost invariably accompanied by hilar or mediastinal lymphadenopathy due to the spread of bacilli from the lung parenchyma

through lymphatic vessels. Enlarged lymph nodes may compress bronchi, causing obstruction and subsequent segmental or lobar collapse. Partial obstruction may cause obstructive emphysema, and bronchiectasis may also develop. Hematogenous dissemination, which is common and is often asymptomatic, may result in the most severe manifestations of primary *M. tuberculosis* infection. Bacilli reach the bloodstream from the pulmonary lesion or the lymph nodes and disseminate into various organs, where they may produce granulomatous lesions. Although healing frequently takes place, immunocompromised persons (e.g., patients with HIV infection and those recovering from measles) may develop miliary tuberculosis and/or tuberculous meningitis.

*Postprimary Disease* Also called adult-type, reactivation, or secondary tuberculosis, postprimary disease results from endogenous reactivation of latent infection and is usually localized to the apical and posterior segments of the upper lobes, where the high oxygen concentration favors mycobacterial growth (Fig. 169-CD1). In addition, the superior segments of the lower lobes are frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. With cavity formation, liquefied necrotic contents are ultimately discharged into the airways, resulting in satellite lesions within the lungs that may in turn undergo cavitation. Massive involvement of pulmonary segments or lobes, with coalescence of lesions, produces tuberculous pneumonia. While up to one-third of untreated patients reportedly succumb to severe pulmonary tuberculosis within a few weeks or months after onset, others undergo a process of spontaneous remission or proceed along a chronic, progressively debilitating course ("consumption"). Under these circumstances, some pulmonary lesions become fibrotic and may later calcify, but cavities persist in other parts of the lungs. Individuals with such chronic disease continue to discharge tubercle bacilli into the environment. Most patients respond to treatment, with defervescence, decreasing cough, weight gain, and a general improvement in well-being within several weeks.

Early in the course of disease, symptoms and signs are often nonspecific and insidious, consisting mainly of fever and night sweats, weight loss, anorexia, general malaise, and weakness. However, in the majority of cases, cough eventually develops -- perhaps initially nonproductive and subsequently accompanied by the production of purulent sputum. Blood streaking of the sputum is frequently documented. Massive hemoptysis may ensue as a consequence of the erosion of a fully patent vessel located in the wall of a cavity. Hemoptysis, however, may also result from rupture of a dilated vessel in a cavity (*Rasmussen's aneurysm*) or from aspergilloma formation in an old cavity. Pleuritic chest pain sometimes develops in patients with subpleural parenchymal lesions but can also result from muscle strain due to persistent coughing. Extensive disease may produce dyspnea and (occasionally) adult respiratory distress syndrome (ARDS).

Physical findings are of limited use in pulmonary tuberculosis. Many patients have no abnormalities detectable by chest examination, while others have detectable rales in the involved areas during inspiration, especially after coughing. Occasionally, rhonchi due to partial bronchial obstruction and classic amphoric breath sounds in areas with large cavities may be heard. Systemic features include fever (often low-grade and intermittent) and wasting. In some cases, pallor and finger clubbing develop. The most common hematologic findings are mild anemia and leukocytosis. Hyponatremia due to

the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has also been reported.

**Extrapulmonary Tuberculosis** In order of frequency, the extrapulmonary sites most commonly involved in tuberculosis are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, and peritoneum. However, virtually all organ systems may be affected. As a result of hematogenous dissemination in HIV-infected individuals, extrapulmonary tuberculosis is seen more commonly today than in the past.

*Lymph-Node Tuberculosis (Tuberculous Lymphadenitis)* The commonest presentation of extrapulmonary tuberculosis (being documented in more than 25% of cases), lymph-node disease is particularly frequent among HIV-infected patients. In the United States, children and women (particularly non-Caucasians) also seem to be especially susceptible. Lymph-node tuberculosis presents as painless swelling of the lymph nodes, most commonly at cervical and supraclavicular sites. Lymph nodes are usually discrete in early disease but may be inflamed and have a fistulous tract draining caseous material (Fig. 169-CD2). Systemic symptoms are usually limited to HIV-infected patients, and concomitant lung disease may or may not be present. The diagnosis is established by fine-needle aspiration or surgical biopsy.AFB are seen in up to 50% of cases, cultures are positive in 70 to 80%, and histologic examination shows granulomatous lesions. Among HIV-infected patients, granulomas are usually not seen. Differential diagnosis includes a variety of infectious conditions as well as neoplastic diseases such as lymphomas or metastatic carcinomas (Chap. 63).

*Pleural Tuberculosis* Involvement of the pleura is common in primary tuberculosis and results from penetration by a few tubercle bacilli into the pleural space. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. A chest radiograph reveals the effusion and, in no more than one-third of cases, also shows a parenchymal lesion. Thoracentesis is required to ascertain the nature of the effusion. The fluid is straw colored and at times hemorrhagic; it is an exudate with a protein concentration >50% of that in serum, a normal to low glucose concentration, a pH that is generally<7.2, and detectable white blood cells (usually 500 to 2500/mL). Neutrophils may predominate in the early stage, while mononuclear cells are the typical finding later. Mesothelial cells are generally rare or absent.AFB are very rarely seen on direct smear, but cultures may be positive for *M. tuberculosis* in up to one-third of cases. Needle biopsy of the pleura is often required for diagnosis and reveals granulomas and/or yields a positive culture in up to 70% of cases. This form of pleural tuberculosis responds well to chemotherapy and may resolve spontaneously.

Tuberculous empyema is a less common complication of pulmonary tuberculosis. It is usually the result of the rupture of a cavity, with delivery of a large number of organisms into the pleural space, or of a bronchopleural fistula from a pulmonary lesion. A chest radiograph may show pyopneumothorax with an air-fluid level. The effusion is purulent and thick and contains large numbers of lymphocytes. An acid-fast smear of pleural fluid is often found to be positive when examined by microscopy, as is culture of the pleural fluid. Surgical drainage is usually required as an adjunct to chemotherapy. Tuberculous

empyema may result in severe pleural fibrosis and restrictive lung disease.

*Tuberculosis of the Upper Airways* Nearly always a complication of advanced cavitary pulmonary tuberculosis (Fig. 169-CD3), tuberculosis of the upper airways may involve the larynx, pharynx, and epiglottis. Symptoms include hoarseness and dysphagia in addition to chronic productive cough. Findings depend on the site of involvement, and ulcerations may be seen on laryngoscopy. Acid-fast smear of the sputum is often positive, but biopsy may be necessary in some cases to establish the diagnosis. Cancer may have similar features but is usually painless.

*Genitourinary Tuberculosis* Genitourinary tuberculosis accounts for about 15% of all extrapulmonary cases, may involve any portion of the genitourinary tract, and is usually due to hematogenous seeding following primary infection. Local symptoms predominate. Urinary frequency, dysuria, hematuria, and flank pain are common presentations. However, patients may be asymptomatic and the disease discovered only after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria. The documentation of culture-negative pyuria in acidic urine raises the suspicion of tuberculosis. An intravenous pyelogram helps in diagnosis. Calcifications and ureteral strictures are suggestive findings. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% of cases. Severe ureteral strictures may lead to hydronephrosis and renal damage.

Genital tuberculosis is diagnosed more commonly in females than in males. In females, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilatation and curettage. In males, tuberculosis preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and prostatitis may also develop. In almost half of cases of genitourinary tuberculosis, urinary tract disease is also present. Genitourinary tuberculosis responds well to chemotherapy.

*Skeletal Tuberculosis* In the United States, tuberculosis of the bones and joints is responsible for about 10% of extrapulmonary cases. In bone and joint disease, pathogenesis is related to reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (spine, hips, and knees -- in that order) are affected most commonly. Spinal tuberculosis (Pott's disease or tuberculous spondylitis) often involves two or more adjacent vertebral bodies. While the upper thoracic spine is the most common site of spinal tuberculosis in children, the lower thoracic and upper lumbar vertebrae are usually affected in adults. From the anterior superior or inferior angle of the vertebral body, the lesion reaches the adjacent body, also destroying the intervertebral disk. With advanced disease, collapse of vertebral bodies results in kyphosis (*gibbus*). A paravertebral "cold" abscess may also form. In the upper spine, this abscess may track to the chest wall as a mass; in the lower spine, it may reach the inguinal ligaments or present as a psoas abscess. Computed tomography (CT) or magnetic resonance imaging (MRI) reveals the characteristic lesion and suggests its etiology, although the differential diagnosis includes other infections and tumors. Aspiration of the abscess or bone biopsy confirms the tuberculous etiology, as cultures are usually positive and histologic findings highly typical. A catastrophic

complication of Pott's disease is paraplegia, which is usually due to an abscess or a lesion compressing the spinal cord. Paraparesis due to a large abscess is a medical emergency and requires abscess drainage. Tuberculosis of the hip joints causes pain and limping; tuberculosis of the knee produces pain and swelling and sometimes follows trauma. If the disease goes unrecognized, the joints may be destroyed. Skeletal tuberculosis responds to chemotherapy, but severe cases may require surgery.

*Tuberculous Meningitis and Tuberculoma* Tuberculosis of the central nervous system accounts for about 5% of extrapulmonary cases. It is seen most often in young children but also develops in adults, especially those who are infected with HIV. Tuberculous meningitis results from the hematogenous spread of primary or postprimary pulmonary disease or from the rupture of a subependymal tubercle into the subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on chest radiography. The disease may present subtly as headache and mental changes or acutely as confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1 or 2 weeks, a course longer than that of bacterial meningitis. Paresis of cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of cerebral arteries may produce focal ischemia. Hydrocephalus is common. Lumbar puncture is the cornerstone of diagnosis. In general, examination of the cerebrospinal fluid (CSF) reveals a high leukocyte count (usually with a predominance of lymphocytes but often with a predominance of neutrophils in the early stage), a protein content of 1 to 8 g/L (100 to 800 mg/dL), and a low glucose concentration; however, any of these three parameters can be within the normal range.AFB are seen on direct smear of CSF sediment in only 20% of cases, but repeated lumbar punctures increase the yield. Culture of CSF is diagnostic in up to 80% of cases. Imaging studies (CT andMRI) may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma. If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Clinical trials have demonstrated that patients treated with adjunctive glucocorticoids experience a significantly faster resolution of CSF abnormalities and elevated CSF pressure. Adjunctive glucocorticoids enhance survival and reduce the frequency of neurologic sequelae.

Tuberculoma, an uncommon manifestation of tuberculosis, presents as one or more space-occupying lesions and usually causes seizures and focal signs.CT orMRIreveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

*Gastrointestinal Tuberculosis* Any portion of the gastrointestinal tract may be affected by tuberculosis. Various pathogenetic mechanisms are involved: swallowing of sputum with direct seeding, hematogenous spread, or (although rarely today) ingestion of milk from cows affected by bovine tuberculosis. The terminal ileum and the cecum are the sites most commonly involved. Abdominal pain (at times similar to that associated with appendicitis), diarrhea, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, and night sweats are also frequent. With intestinal-wall involvement, ulcerations and fistulae may simulate Crohn's disease. Anal fistulae should prompt an evaluation for rectal tuberculosis. As surgery is required in most cases, the diagnosis can be established by histologic examination and culture of specimens obtained intraoperatively.

Tuberculous peritonitis follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intraabdominal organs or hematogenous seeding. Nonspecific abdominal pain, fever, and ascites should raise the suspicion of tuberculous peritonitis. The coexistence of cirrhosis (Chap. 298) in patients with tuberculous peritonitis complicates the diagnosis. In tuberculous peritonitis, paracentesis reveals an exudative fluid with a high protein content and leukocytosis that is usually lymphocytic (although neutrophils occasionally predominate). The yield of direct smear and culture is relatively low; culture of a large volume of ascitic fluid can increase the yield, but peritoneal biopsy is often needed to establish the diagnosis.

*Pericardial Tuberculosis (Tuberculous Pericarditis)* Due to direct progression of a primary focus within the pericardium, to reactivation of a latent focus, or to rupture of an adjacent lymph node, pericardial tuberculosis has often been a disease of the elderly in countries with low tuberculosis prevalence but develops frequently in HIV-infected patients. Case-fatality rates are as high as 40% in some series. The onset may be subacute, although an acute presentation, with fever, dull retrosternal pain, and a friction rub, is possible. An effusion eventually develops in many cases; cardiovascular symptoms and signs of cardiac tamponade may ultimately appear (Chap. 239). In the presence of effusion detected on chest radiography, tuberculosis must be suspected if the patient belongs to a high-risk population (HIV-infected, originating in a high-prevalence country), if there is evidence of previous tuberculosis or disease in other organs, or if echocardiography shows thick strands crossing the pericardial space. Diagnosis can be facilitated by pericardiocentesis under echocardiographic guidance. The pericardial fluid must be submitted for biochemical, cytologic, and microbiologic study. The effusion is exudative in nature, with a high count of leukocytes (predominantly mononuclear cells). Hemorrhagic effusion is frequent. Culture of the fluid reveals *M. tuberculosis* in about 30% of cases, while biopsy has a higher yield. Without treatment, pericardial tuberculosis is usually fatal. Even with treatment, complications may develop, including chronic constrictive pericarditis with thickening of the pericardium, fibrosis, and sometimes calcification, which may be visible on a chest radiograph. A course of glucocorticoid treatment is useful in the management of acute disease, reducing effusion, facilitating hemodynamic recovery, and thus decreasing mortality. Progression to chronic constrictive pericarditis, however, seems unaffected by such therapy.

*Miliary or Disseminated Tuberculosis* Miliary tuberculosis is due to hematogenous spread of tubercle bacilli. Although in children it is often the consequence of a recent primary infection, in adults it may be due to either recent infection or reactivation of old disseminated foci. Lesions are usually yellowish granulomas 1 to 2 mm in diameter that resemble millet seeds (thus the term *miliary*, coined by nineteenth-century pathologists).

Clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases. At times, patients have a cough and other respiratory symptoms due to pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary tuberculosis, in up to 30% of cases. Meningismus occurs in fewer than 10% of cases.

A high index of suspicion is required for the diagnosis of miliary tuberculosis. Frequently, chest radiography (Fig. 169-CD5) reveals a miliary reticulonodular pattern (more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among HIV-infected patients. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in HIV-infected patients), and pleural effusion. A sputum smear is negative in 80% of cases. Various hematologic abnormalities may be seen, including anemia with leukopenia, neutrophilic leukocytosis and leukemoid reactions, and polycythemia. Disseminated intravascular coagulation has been reported. Elevation of alkaline phosphatase levels and other abnormal values in liver function tests are detected in patients with severe hepatic involvement. The PPDtest may be negative in up to half of cases, but reactivity may be restored during chemotherapy. Bronchoalveolar lavage and transbronchial biopsy are more likely to permit bacteriologic confirmation, and granulomas are evident in liver or bone-marrow biopsy specimens from many patients. If it goes unrecognized, miliary tuberculosis is lethal; with proper treatment, however, it is amenable to cure.

A rare presentation seen in the elderly is *cryptic miliary tuberculosis*, which has a chronic course characterized by mild intermittent fever, anemia, and -- ultimately -- meningeal involvement preceding death. An acute septicemic form, *nonreactive miliary tuberculosis*, occurs very rarely and is due to massive hematogenous dissemination of tubercle bacilli. Pancytopenia is common in this form of disease, which is rapidly fatal. At postmortem examination, multiple necrotic but nongranulomatous ("nonreactive") lesions are detected.

*Less Common Extrapulmonary Forms* Tuberculosis may cause chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis. Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation. In the nasopharynx, tuberculosis may simulate Wegener's granulomatosis. Cutaneous manifestations of tuberculosis include primary infection due to direct inoculation, abscesses and chronic ulcers, scrofuloderma (Fig. 169-CD2), lupus vulgaris (Fig. 169-CD4), miliary lesions, and erythema nodosum. Adrenal tuberculosis is a manifestation of advanced disease presenting as signs of adrenal insufficiency. Finally, congenital tuberculosis results from transplacental spread of tubercle bacilli to the fetus or from ingestion of contaminated amniotic fluid. This rare disease affects the liver, spleen, lymph nodes, and various other organs.

**HIV-Associated Tuberculosis** Tuberculosis is an important opportunistic disease among HIV-infected persons worldwide. In developing countries of Africa, Southeast Asia, and Latin America, an estimated 10 million persons were coinfected as of 1997. In the United States, coinfection with HIV and *M. tuberculosis* is common in certain segments of the population, including drug users and some minorities. A person with skin test-documented *M. tuberculosis* infection who acquires HIV infection has a 3 to 15% annual risk of developing active tuberculosis.

The association between tuberculosis and HIV infection is supported by other epidemiologic observations. First, the rate of HIV seropositivity among patients with tuberculosis is several times higher than that among the general population: in African countries it reaches 60 to 70%. Second, marked increases in numbers of tuberculosis

cases have been reported at locations hard hit by the HIV epidemic, such as large parts of Africa (including Kenya, Tanzania, and Malawi), northern Thailand, and New York City. Globally, the proportion of tuberculosis cases associated with HIV infection reached 8% in 1997.

HIV directly attacks the critical immune mechanisms involved in protection against tuberculosis. Tuberculosis can appear at any stage of HIV infection, but its presentation varies with the stage. When cell-mediated immunity is only partially compromised, pulmonary tuberculosis presents as a typical pattern of upper lobe infiltrates and cavitation, without significant lymphadenopathy or pleural effusion. In late stages of HIV infection, a primary tuberculosis-like pattern, with diffuse interstitial or miliary infiltrates, little or no cavitation, and intrathoracic lymphadenopathy, is more common. Overall, sputum smears may be positive less frequently among tuberculosis patients with HIV infection than among those without; thus the diagnosis of tuberculosis may be unusually difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking tuberculosis.

As has been mentioned, extrapulmonary tuberculosis is common among HIV-infected patients. In various series studied in the United States and many developing countries, extrapulmonary tuberculosis -- alone or in association with pulmonary disease -- has been documented in 40 to 60% of all cases in HIV co-infected individuals. The most common forms are lymphatic, disseminated, pleural, and pericardial. Mycobacteremia and meningitis are also frequent, particularly in advanced HIV disease.

The diagnosis of tuberculosis in HIV-infected patients may be difficult not only because of the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also because of atypical radiographic findings, a lack of classic granuloma formation in the late stages, and negative results inPPD skin tests. Delays in treatment may prove fatal. The response to short-course chemotherapy is similar to that in HIV-seronegative patients. However, adverse effects may be more pronounced, including severe or even fatal skin reactions to amithiozone (thiacetazone).

Exacerbations in symptoms, signs, and laboratory or radiographic manifestations of tuberculosis -- termed *paradoxical reactions* -- have been associated with the administration of highly active antiretroviral treatment (HAART) regimens. The presumed pathogenesis of paradoxical reactions is an immune response to antigens released as bacilli are killed by effective chemotherapy. In patients in whom antiretroviral therapy has recently been started, paradoxical reactions may be due to improving immune function. The first priority in the management of a possible paradoxical reaction is to ensure that the clinical syndrome does not represent a failure of tuberculosis treatment or the development of another infection. Mild paradoxical reactions can be managed with symptom-based treatment. More severe manifestations may necessitate discontinuation of antiretroviral therapy. Immunomodulators, such as glucocorticoids, have been used to treat severe paradoxical reactions, although this practice has not been formally evaluated in clinical trials.

Recommendations for the prevention and treatment of tuberculosis in HIV-infected individuals have been published by theCDC.

## DIAGNOSIS

The key to the diagnosis of tuberculosis is a high index of suspicion. Diagnosis is not difficult with a high-risk patient -- e.g., a homeless alcoholic who presents with typical symptoms and a classic chest radiograph showing upper lobe infiltrates with cavities. On the other hand, the diagnosis can easily be missed in an elderly nursing-home resident or a teenager with a focal infiltrate.

Often, the diagnosis is first entertained when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical conditions that favor immunosuppression, the chest radiograph may show the typical picture of upper lobe infiltrates with cavitation. The longer the delay between the onset of symptoms and the diagnosis, the more likely is the finding of cavitary disease. In contrast, immunosuppressed patients, including those with HIV infection, may have "atypical" findings on chest radiography -- e.g., lower zone infiltrates without cavity formation.

**AFB Microscopy** A presumptive diagnosis is commonly based on the finding of AFB on microscopic examination of a diagnostic specimen such as a smear of expectorated sputum or of tissue (for example, a lymph node biopsy). Most modern laboratories processing large numbers of diagnostic specimens use auramine-rhodamine staining and fluorescence microscopy. The more traditional method -- light microscopy of specimens stained with Kinyoun or Ziehl-Neelsen basic fuchsin dyes -- is satisfactory, although more time-consuming. For patients with suspected pulmonary tuberculosis, three sputum specimens, preferably collected early in the morning, should be submitted to the laboratory for AFB smear and mycobacteriology culture. If tissue is obtained, it is critical that the portion of the specimen intended for culture not be put in formaldehyde. The use of AFB microscopy on urine or gastric lavage fluid is limited by the presence of mycobacterial commensals, which can cause false-positive results.

**Mycobacterial Culture** Definitive diagnosis depends on the isolation and identification of *M. tuberculosis* from a diagnostic specimen -- in most cases, a sputum specimen obtained from a patient with a productive cough. Specimens may be inoculated onto egg- or agar-based medium (e.g., Lowenstein-Jensen or Middlebrook 7H10) and incubated at 37°C under 5% $CO_2$. Because most species of mycobacteria, including *M. tuberculosis*, grow slowly, 4 to 8 weeks may be required before growth is detected. Although *M. tuberculosis* may be presumptively identified on the basis of growth time and colony pigmentation and morphology, a variety of biochemical tests have traditionally been used to speciate mycobacterial isolates. In today's laboratories, the use of liquid media with radiometric growth detection (e.g., BACTEC-460) and the identification of isolates by nucleic acid probes or high-pressure liquid chromatography of mycolic acids have replaced the traditional methods of isolation on solid media and identification by biochemical tests. These new methods have decreased the time required for isolation and speciation to 2 to 3 weeks. Other systems for culture on liquid media with nonradiometric detection have become available.

**Nucleic Acid Amplification** Several test systems based on amplification of mycobacterial nucleic acid are available. These systems permit the diagnosis of tuberculosis in as short a period as several hours. However, their applicability is limited

by low sensitivity (lower than culture) and high cost. At present, these tests are approved by the U.S. Food and Drug Administration only for species identification onAFB-positive sputa. With further improvements in performance, these tests may also be useful for the diagnosis of patients with AFB-negative pulmonary and extrapulmonary tuberculosis.

**Radiographic Procedures** As noted above, the initial suspicion of pulmonary tuberculosis is often based on abnormal chest radiographic findings in a patient with respiratory symptoms. Although the "classic" picture is that of upper lobe disease with infiltrates and cavities, virtually any radiographic pattern -- from a normal film or a solitary pulmonary nodule to diffuse alveolar infiltrates in a patient withARDS -- may be seen. In the era of AIDS, no radiographic pattern can be considered pathognomonic.

**PPDSkin Testing** Skin testing with PPD is most widely used in screening for *M. tuberculosis* infection (see below). The test is of limited value in the diagnosis of active tuberculosis because of its low sensitivity and specificity. False-negative reactions are common in immunosuppressed patients and in those with overwhelming tuberculosis. Positive reactions are obtained when patients have been infected with *M. tuberculosis* but do not have active disease and when persons have been sensitized by nontuberculous mycobacteria (Chap. 171) or bacille Calmette-Guerin (BCG) vaccination. Although BCG vaccine is not commonly used in the United States, many immigrants will have received it. In the absence of a history of BCG vaccination, a positive skin test may provide additional support for the diagnosis of tuberculosis in culture-negative cases.

**Drug Susceptibility Testing** In general, the initial isolate of *M. tuberculosis* should be tested for susceptibility to the primary drugs used for treatment: isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin. In addition, drug susceptibility tests are mandatory when patients fail to respond to initial therapy or experience a relapse after the completion of treatment (see below). Susceptibility testing may be conducted directly (with the clinical specimen) or indirectly (with mycobacterial cultures) on solid or liquid medium. Results are obtained most rapidly by direct susceptibility testing on liquid medium, with an average reporting time of 3 weeks. With indirect testing on solid media, results may not be available for 8 weeks or longer. Molecular methods for the rapid identification of drug resistance are becoming available. One of the most promising uses polymerase chain reaction (PCR) for the *rpoB* gene to detect resistance to rifampin.

**Additional Diagnostic Procedures** Other diagnostic tests may be used when pulmonary tuberculosis is suspected. Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients unable to produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e.g., bronchogenic carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings or transbronchial biopsy of the lesion. Bronchoalveolar lavage of a lung segment containing an abnormality may also be performed. In all cases, it is essential that specimens be submitted forAFBsmear and mycobacterial culture. For the diagnosis of primary pulmonary tuberculosis in children, who often do not expectorate sputum, specimens from early-morning gastric lavage may yield positive cultures.

Invasive diagnostic procedures are indicated for patients with suspected extrapulmonary

tuberculosis. In addition to specimens of involved sites (e.g.,CSF for tuberculous meningitis, pleural fluid and biopsy samples for pleural disease), bone marrow and liver biopsy and culture have a good diagnostic yield in disseminated (miliary) tuberculosis, particularly in HIV-infected patients, who also have a high frequency of positive blood cultures.

In some cases, cultures will be negative, but a clinical diagnosis of tuberculosis will be supported by consistent epidemiologic evidence (e.g., a history of close contact with an infectious patient), a positivePPD skin test, and a compatible clinical and radiographic response to treatment. In the United States and other industrialized countries with low rates of tuberculosis, some patients with limited abnormalities on chest radiographs and sputum positive forAFB are infected with organisms of the *M. avium* complex or *M. kansasii* (Chap. 171). Factors favoring the diagnosis of nontuberculous mycobacterial disease over tuberculosis include an absence of risk factors for tuberculosis, a negative PPD skin test, and underlying chronic obstructive pulmonary disease.

Patients with HIV-associated tuberculosis pose several diagnostic problems, as noted above in the description of clinical manifestations. Moreover, HIV-infected patients with sputum culture-positive andAFB-positive tuberculosis may present with a normal chest radiograph. Thus, in a patient with HIV infection, the finding of a normal chest radiograph does not rule out the diagnosis of pulmonary tuberculosis. An additional consideration is that, among relatively severely immunosuppressed AIDS patients in Europe and North America, *M. avium* complex disease is more common than tuberculosis, usually presenting as a disseminated disease without pulmonary parenchymal involvement.

**Adjunctive Diagnostic Tests** A number of methods have been evaluated as adjuncts to standard laboratory diagnosis. The most thoroughly investigated is serologic diagnosis based on detection of antibody to a variety of mycobacterial antigens. However, tests with most of the target antigens have a low predictive value when used in a population with a presumably low probability of disease. Tests aimed at detection of mycobacterial antigen by serologic methods have generally not been sufficiently sensitive to be useful. Nonspecific tests, such as the measurement of adenine deaminase in pleural fluid, have been evaluated but have not gained acceptance.

## TREATMENT

Chemotherapy for tuberculosis became possible with the discovery of streptomycin in the mid-1940s. Randomized clinical trials clearly indicated that the administration of streptomycin to patients with chronic tuberculosis reduced mortality and led to cure in the majority of cases. However, monotherapy with streptomycin was frequently associated with the development of resistance to streptomycin and the attendant failure of treatment. With the discovery of para-aminosalicylic acid (PAS) and isoniazid, it became axiomatic that cure of tuberculosis required the concomitant administration of at least two agents to which the organism was susceptible. Furthermore, early clinical trials demonstrated that a long period of treatment -- i.e., 12 to 24 months -- was required to prevent the recurrence of tuberculosis.

The introduction of rifampin in the early 1970s heralded the era of effective short-course

chemotherapy, with a treatment duration of <12 months. The discovery that pyrazinamide, which was first used in the 1950s, augmented the potency of isoniazid/rifampin regimens led to the use of a 6-month course of this triple-drug regimen as standard therapy.

**Drugs** Five major drugs are considered the first-line agents for the treatment of tuberculosis: isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin (Table 169-1). The first four, which are usually given orally, are well absorbed, with peak serum levels at 2 to 4 h and nearly complete elimination within 24 h. These agents are recommended on the basis of their bactericidal activity (ability to rapidly reduce the number of viable organisms), their sterilizing activity (ability to kill all bacilli and thus sterilize the affected organ, measured in terms of the ability to prevent relapses), and their low rate of induction of drug resistance. Rifapentine and rifabutin, two drugs related to rifampin, are also available in the United States.*For a detailed discussion of the drugs used for the treatment of tuberculosis, see Chap. 168.*

Because of a lower degree of efficacy and a higher degree of intolerability and toxicity, a number of second-line drugs are used only for the treatment of patients with tuberculosis resistant to first-line drugs. Included in this group are the injectable drugs kanamycin, amikacin, and capreomycin and the oral agents ethionamide, cycloserine, andPAS. Recently, quinolone antibiotics have become the most commonly used second-line drugs. Of available agents, ofloxacin is the most widely used, but levofloxacin and sparfloxacin are the most active, although the latter drug is associated with high rates of photosensitization. Other second-line drugs include clofazimine, amithiozone (thiacetazone, widely used with isoniazid in less wealthy countries but not marketed in North America or Europe), and amoxicillin/clavulanic acid.

**Regimens** Short-course regimens are divided into an initial or bactericidal phase and a continuation or sterilizing phase. During the initial phase, the majority of the tubercle bacilli are killed, symptoms resolve, and the patient becomes noninfectious. The continuation phase is required to eliminate semidormant "persisters."

The treatment regimen of choice for virtually all forms of tuberculosis in both adults and children consists of a 2-month initial phase of isoniazid, rifampin, and pyrazinamide followed by a 4-month continuation phase of isoniazid and rifampin (Table 169-2). Except for patients who seem unlikely on epidemiologic grounds to be initially infected with a drug-resistant strain, ethambutol (or streptomycin) should be included in the regimen for the first 2 months or until the results of drug susceptibility testing become available. Treatment may be given daily throughout the course or intermittently (either three times weekly throughout the course or twice weekly following an initial phase of daily therapy). A continuation phase of once-weekly rifapentine and isoniazid appears to be effective for patients who have adhered to the initial-phase treatment and have negative sputum cultures at 2 months. Intermittent treatment is especially useful for patients whose therapy is being directly observed (see below). For patients with sputum culture-negative pulmonary tuberculosis, the duration of treatment may be reduced to a total of 4 months. Pyridoxine (10 to 25 mg/d) should be added to the regimen given to persons at high risk of vitamin deficiency (e.g., alcoholics; malnourished persons; pregnant and lactating women; and patients with conditions such as chronic renal failure, diabetes, and HIV infection or AIDS, which are also associated with neuropathy).

Lack of adherence to treatment regimens is recognized worldwide as the most important impediment to cure. Moreover, the mycobacterial strains infecting patients who do not adhere to the prescribed regimen are especially likely to develop acquired drug resistance. Both patient- and provider-related factors may affect compliance. Patient-related factors include a lack of belief that the illness is significant and/or that treatment will have a beneficial effect; the existence of concomitant medical conditions (notably substance abuse); lack of social support; and poverty, with attendant joblessness and homelessness. Provider-related factors that may promote compliance include the education and encouragement of patients, the offering of convenient clinic hours, and the provision of incentives such as bus tokens.

In addition to specific measures addressing noncompliance, two other strategic approaches are used: direct observation of treatment and provision of drugs in combined formulations. Because it is difficult to predict which patients will adhere to the recommended treatment, all patients should have their therapy directly supervised, especially during the initial phase. In the United States, personnel to supervise therapy are usually available through tuberculosis control programs of local public health departments. Supervision increases the proportion of patients completing treatment and greatly lessens the chances of relapse and acquired drug resistance. Combination products (e.g., isoniazid/rifampin and isoniazid/rifampin/pyrazinamide) are available and are strongly recommended as a means of minimizing the likelihood of prescription error and of the development of drug resistance (as the result of treatment with only one agent). In some formulations of these combination products, the bioavailability of rifampin has been found to be substandard. In North America and Europe, regulatory authorities ensure that combination products are of good quality; however, this type of monitoring cannot be assumed to take place in less affluent countries. Alternative regimens for patients who exhibit drug intolerance or adverse reactions are listed inTable 169-2. However, severe side effects prompting discontinuation of any of the first-line drugs and use of these alternative regimens are uncommon.

**Monitoring the Response to Treatment** Bacteriologic evaluation is the preferred method of monitoring the response to treatment for tuberculosis. Patients with pulmonary disease should have their sputum examined monthly until cultures become negative. With the recommended 6-month regimen, more than 80% of patients will have negative sputum cultures at the end of the second month of treatment. By the end of the third month, virtually all patients should be culture-negative. In some patients, especially those with extensive cavitary disease and large numbers of organisms,AFBsmear conversion may follow culture conversion. This phenomenon is presumably due to the expectoration and microscopic visualization of dead bacilli. When a patient's sputum cultures remain positive at or beyond 3 months, treatment failure and drug resistance should be suspected (see below). A sputum specimen should be collected at the end of treatment to document cure. If mycobacterial cultures are not practical, then monitoring by AFB smear examination should be undertaken at 2, 5, and 6 months. Smears positive after 5 months are indicative of treatment failure.

Bacteriologic monitoring of patients with extrapulmonary tuberculosis is more difficult and often is not feasible. In these cases, the response to treatment must be assessed clinically.

Monitoring of the response to treatment during chemotherapy by serial chest radiographs is not recommended, as radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treatment, neither sputum examination nor chest radiography is recommended for follow-up purposes. However, a chest radiograph may be obtained at the end of treatment and used for comparative purposes should the patient develop symptoms of recurrent tuberculosis months or years later. Patients should be instructed to report promptly for medical assessment should they develop any such symptoms.

During treatment, patients should be monitored for drug toxicity (see alsoTable 168-3). The most common adverse reaction of significance is hepatitis. Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite) and should be instructed to discontinue treatment promptly and see their health care provider should these symptoms occur. Although biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function (e.g., measurement of levels of hepatic aminotransferases and serum bilirubin). Older patients, those with histories of hepatic disease, and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment. Up to 20% of patients have small increases in aspartate aminotransferase (up to three times the upper limit of normal) that are accompanied by no symptoms and are of no consequence. For patients with symptomatic hepatitis and those with marked (five- to sixfold) elevations in aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal.

Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit. Because of the variety of regimens available, it is usually not necessary -- although it is possible -- to desensitize patients. Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis. Individuals who develop autoimmune thrombocytopenia secondary to rifampin therapy should not receive the drug thereafter. Similarly, the occurrence of optic neuritis with ethambutol and the development of eighth-nerve damage with streptomycin are indications for permanent discontinuation of these respective drugs. Other common manifestations of drug intolerance, such as pruritus and gastrointestinal upset, can generally be managed without the interruption of therapy.

**Treatment Failure and Relapse** As stated above, treatment failure should be suspected when a patient's sputum cultures remain positive after 3 months or whenAFBsmears remain positive after 5 months. In the management of such patients, it is imperative that the current isolate be tested for susceptibility to first- and second-line agents. When the results of susceptibility testing are expected to become available within a few weeks, changes in the regimen can be postponed until that time. However, if the patient's clinical condition is deteriorating, an earlier change in regimen may be indicated. A cardinal rule in the latter situation is always to add more than one drug at a time to a failing regimen: at least two and preferably three drugs that have never been used should be added. The patient may continue to take isoniazid and rifampin along

with these new agents pending the results of susceptibility tests.

The mycobacterial strains infecting patients who experience a relapse after apparently successful treatment are less likely to have acquired drug resistance (see below) than are strains from patients in whom treatment has failed. However, if the regimen administered initially does not contain rifampin (and thus is not a short-course regimen), the probability of isoniazid resistance is high. Acquired resistance is uncommon among strains from patients who relapse after completing a short course of therapy. However, it is prudent to begin the treatment of all relapses with all five first-line drugs pending the results of susceptibility testing. In less affluent countries and other settings where facilities for culture and drug susceptibility testing are not available, a standard regimen should be used in all instances of relapse and treatment failure (Table 169-2).

**Adjunctive Glucocorticoid Therapy** The use of glucocorticoids for adjunctive treatment of tuberculosis is justified by their potent anti-inflammatory activity in a disease where host response plays a major role. There is a sound basis for using glucocorticoids in tuberculous meningitis and pericarditis to hasten clinical improvement (see above). Long-term benefits are limited to reduced mortality in effusive-constrictive pericarditis and decreased neurologic sequelae in meningitis. Studies have indicated that the usefulness of these agents in pleuritis may be less important than previously thought. There is not yet conclusive evidence that glucocorticoids produce benefits in patients with acute life-threatening pulmonary tuberculosis, includingARDS. In general, depending upon the urgency and severity of clinical conditions, prednisone may be administered at a daily dose of 20 to 60 mg for up to 6 weeks. In meningitis, dexamethasone (up to 12 mg/d) is the preferred drug; therapy continues for 4 to 6 weeks, with gradual tapering of the dose after the first 2 weeks. Rifampin interaction with glucocorticoids, resulting in accelerated metabolism and potential adrenal crisis, must be taken into account. Caution should be exercised in the use of glucocorticoids in HIV-infected patients.

**Drug-Resistant Tuberculosis** Strains of *M. tuberculosis* resistant to individual drugs arise by spontaneous point mutations in the mycobacterial genome, which occur at low but predictable rates. Because there is no cross-resistance among the commonly used drugs, the probability that a strain will be resistant to two drugs is the product of the probabilities of resistance to each drug and thus is low. The development of drug-resistant tuberculosis is invariably the result of monotherapy -- i.e., the failure of the health care provider to prescribe at least two drugs to which tubercle bacilli are susceptible or of the patient to take properly prescribed therapy.

Drug-resistant tuberculosis may be either primary or acquired. *Primary* drug resistance is that in a strain infecting a patient who has not previously been treated. *Acquired* resistance develops during treatment with an inappropriate regimen. In North America and Europe, rates of primary resistance are generally low, and isoniazid resistance is most common. In the United States, while isoniazid resistance was stable at about 8% in 1993 through 1996, rates ofMDRtuberculosis were declining. Resistance rates are higher among foreign-born and HIV-infected patients. Worldwide, MDR tuberculosis is a serious problem in some regions, especially in the former USSR and parts of Asia. As noted above, drug-resistant tuberculosis can be prevented by adherence to the principles of sound therapy: the inclusion of at least two bactericidal drugs to which the

organism is susceptible (in practice, four drugs are commonly given in the initial phase) and the verification that patients complete the prescribed course.

Although the 6-month regimen described in Table 169-2 is highly effective for patients with initial isoniazid-resistant disease, it is prudent to extend treatment to 9 months and to include ethambutol throughout. Alternatively, rifampin, pyrazinamide, and ethambutol may be given for 6 months. For disease with high-level isoniazid resistance, isoniazid probably does not contribute to a successful outcome and can be omitted.MDRtuberculosis is more difficult to manage than is disease caused by a drug-susceptible organism, especially because resistance to other first-line drugs as well as to isoniazid and rifampin is common. For strains resistant to isoniazid and rifampin, combinations of ethambutol, pyrazinamide, and streptomycin (or, for those resistant to streptomycin as well, another injectable agent such as amikacin), given for 12 to 18 months in all and for at least 9 months after sputum culture conversion, may be effective. Many authorities would add a quinolone antibiotic to this regimen. For patients with bacilli resistant to all of the first-line agents, cure may be attained with a combination of four second-line drugs, including one injectable agent (Table 169-2). The optimal duration of treatment in this situation is not known; however, a duration of up to 24 months is recommended. For patients with localized disease and sufficient pulmonary reserve, lobectomy or pneumonectomy may be helpful. Because the management of patients with MDR tuberculosis is complicated by both social and medical factors, care of these patients should be restricted to specialists and tuberculosis control programs.

**Special Clinical Situations** Although comparative clinical trials of treatment for extrapulmonary tuberculosis are limited, the available evidence indicates that most forms of disease can be treated with the 6-month regimen recommended for patients with pulmonary disease. The American Academy of Pediatrics recommends that children with bone and joint tuberculosis, tuberculous meningitis, or miliary tuberculosis receive a minimum of 12 months of treatment.

Treatment for tuberculosis may be complicated by underlying medical problems that require special consideration (see also Table 168-1). As a rule, patients with chronic renal failure should not receive aminoglycosides and should receive ethambutol only if serum levels can be monitored. Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis. Patients with hepatic disease pose a special problem because of the hepatotoxicity of isoniazid, rifampin, and pyrazinamide. Patients with severe hepatic disease may be treated with ethambutol and streptomycin and, if required, with isoniazid and rifampin under close supervision. The use of pyrazinamide by patients with liver failure should be avoided. Silicotuberculosis necessitates the extension of therapy by at least 2 months. Patients with HIV infection or AIDS appear to respond well to standard 6-month therapy, although treatment may need to be prolonged if the response is suboptimal. Rifampin, a powerful inducer of hepatic microsomal enzymes, shortens the half-life of HIV protease inhibitors and therefore is contraindicated for patients receiving these drugs; instead, these individuals should be given rifabutin (150 mg/d or 300 mg twice weekly) with either indinavir or nelfinavir. Studies have shown that total systemic drug exposure, especially for rifampin, is

reduced in HIV-infected patients because of decreased bioavailability secondary to malabsorption. The clinical importance of this phenomenon remains unclear.

The regimen of choice for pregnant women (see alsoTable 168-1) is 9 months of treatment with isoniazid and rifampin supplemented by ethambutol for the first 2 months. When required, pyrazinamide may be given, although there are no data concerning its safety in pregnancy. Streptomycin is contraindicated because it is known to cause eighth-cranial-nerve damage in the fetus. Treatment for tuberculosis is not a contraindication to breast feeding; most of the drugs administered will be present in small quantities in breast milk, albeit at concentrations far too low to provide any therapeutic or prophylactic benefit to the child.

## PREVENTION

By far the best way to prevent tuberculosis is to diagnose infectious cases rapidly and administer appropriate treatment until cure. Additional strategies includeBCGvaccination and preventive chemotherapy.

**BCG Vaccination** BCG was derived from an attenuated strain of *M. bovis* and was first administered to humans in 1921. Many BCG vaccines are available worldwide; all are derived from the original strain, but the vaccines vary in efficacy. In fact, estimates of efficacy from randomized, placebo-controlled trials have ranged from 80% to nil. A similar range of efficacy was found in recent observational studies (case-control, historic cohort, and cross-sectional) in areas where infants are vaccinated at birth. These studies also found higher rates of efficacy in the protection of infants and young children from relatively serious forms of tuberculosis, such as tuberculous meningitis and miliary tuberculosis.

BCGvaccine is safe and rarely causes serious complications. The local tissue response begins 2 to 3 weeks after vaccination, with scar formation and healing within 3 months. Side effects -- most commonly, ulceration at the vaccination site and regional lymphadenitis -- occur in 1 to 10% of vaccinated persons. Some vaccine strains have caused osteomyelitis in approximately one case per million doses administered. Disseminated BCG infection and death have occurred in 1 to 10 cases per 10 million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity, such as children with severe combined immunodeficiency syndrome (SCIDS) or adults with HIV infection. BCG vaccination inducesPPDreactivity, which tends to wane with time. The presence or size of PPD skin-test reactions after vaccination does not predict the degree of protection afforded.

BCGvaccine is recommended for routine use at birth in countries with high tuberculosis prevalence. However, because of the low risk of transmission of tuberculosis in the United States and the unreliable protection afforded by BCG, the vaccine has never been recommended for general use in the United States. Currently, vaccination should be considered forPPD-negative infants and children who reside in settings where the likelihood of *M. tuberculosis* transmission and subsequent infection is high, provided no other measures can be implemented (e.g., removing the child from the source of infection). BCG vaccination may also be considered for health care workers who are employed in settings where the risk of infection byMDRstrains is high despite

implementation of comprehensive tuberculosis control measures. TheCDC has recommended that HIV-infected adults and children not receive BCG vaccine, although theWHO has recommended that asymptomatic HIV-infected children residing in tuberculosis-endemic areas receive BCG.

**Treatment of Latent Tuberculosis Infection** A major component of tuberculosis control in the United States is the treatment of selected persons with latent tuberculosis infection to prevent active disease. This intervention (formerly called preventive chemotherapy or chemoprophylaxis) is based on the results of a large number of randomized, placebo-controlled clinical trials demonstrating that a 6- to 12-month course of isoniazid reduces the risk of active tuberculosis in infected people by³90%. Analysis of available data indicates that the optimal duration of treatment is 9 to 10 months. In the absence of reinfection, the protective effect is believed to be lifelong. Clinical trials have also shown that isoniazid reduces rates of tuberculosis amongPPD-positive persons with HIV infection. Studies in HIV-infected patients have demonstrated the effectiveness of a shorter course of rifampin-based treatment.

In most cases, candidates for treatment of latent tuberculosis (Table 169-3) are identified byPPD skin testing of persons in defined high-risk groups. For skin testing, 5 tuberculin units of polysorbate-stabilized PPD should be injected intradermally into the volar surface of the forearm (Mantoux method). Multipuncture tests, which may be useful for screening large populations, are not recommended for this purpose; any positive reaction to a multipuncture test must be confirmed by Mantoux testing. Reactions are read at 48 to 72 h as the transverse diameter in millimeters of induration; the diameter of erythema is not considered. In some persons, PPD reactivity wanes with time but can be recalled by a second skin test administered 1 week or more after the first (i.e., two-step testing). For persons undergoing periodic PPD skin testing, such as health care workers and individuals admitted to long-term-care institutions, initial two-step testing may preclude subsequent misclassification of persons with boosted reactions as PPD converters.

The cutoff for a positive skin test (and thus for treatment) is related both to the probability that the reaction represents true infection and to the likelihood that the individual, if truly infected, will develop tuberculosis (Table 169-3). Thus positive reactions for close contacts of infectious cases, persons with HIV infection, and previously untreated persons whose chest radiograph is consistent with healed tuberculosis are defined as an area of induration 5 mm in diameter. A 10-mm cutoff is used to define positive reactions in most other at-risk persons. For persons with a very low risk of developing tuberculosis if infected, a cutoff of 15 mm is used. Persons with a history ofBCGvaccination may receive treatment, especially if BCG was given many years before.

SomePPD-negative individuals are also candidates for treatment. Infants and children who have come into contact with infectious cases should be treated and should have a repeat skin test 2 or 3 months after contact ends. Those whose test results remain negative should discontinue treatment. HIV-infected persons who have been exposed to an infectious tuberculosis patient should receive treatment regardless of the PPD test result.

Isoniazid is administered at a daily dose of 5 mg/kg (up to 300 mg/d) for 9 months. On the basis of cost-benefit analyses, a 6-month period of treatment has been recommended in the past and may be considered for HIV-negative adults with normal chest radiographs when financial considerations are important. When supervised treatment is desirable and feasible, isoniazid may be given at a dose of 15 mg/kg (up to 900 mg) twice weekly. There are two recommended alternative regimens for adults: 2 months of daily rifampin plus pyrazinamide and 4 months of daily rifampin. Although the 2-month regimen may be associated with increased drug intolerance, it may be useful in situations where long courses of isoniazid have not been feasible (e.g., jails). Either regimen should be considered for persons who are likely to have been infected with an isoniazid-resistant strain.

Contraindications to treatment with isoniazid and pyrazinamide include active liver disease. Since the major adverse reaction to these drugs is hepatitis, persons at increased risk of toxicity (e.g., those abusing alcohol daily and those with a history of liver disease) should undergo baseline and then monthly assessment of liver function during treatment. All patients should be carefully educated about hepatitis and instructed to discontinue use of the drug immediately should any symptoms develop. Moreover, patients should be seen and questioned monthly during therapy about adverse reactions and should be given no more than 1 month's supply of drug at each visit.

It may be more difficult to ensure compliance when treating persons with latent infection than when treating those with active tuberculosis. If family members of active cases are being treated, compliance and monitoring may be easier. When feasible, twice-weekly supervised therapy may increase the likelihood of completion. As in active cases, the provision of incentives may also be helpful.

## BASICS OF CONTROL

The highest priority in any tuberculosis control program is the prompt detection of cases and the provision of directly observed short-course chemotherapy to all tuberculosis patients, with emphasis on the cure of sputum smear-positive cases. In addition, in low-prevalence countries with adequate resources, screening of high-risk groups (such as immigrants from high-prevalence countries and HIV-seropositive persons) is recommended. Identification of active cases of tuberculosis should be followed by treatment.PPD-positive high-risk persons should be treated for latent infection. Contact investigation is an important component of efficient tuberculosis control. In the United States, a great deal of attention has been given to the transmission of tuberculosis (particularly in association with HIV infection) in institutional settings such as hospitals, homeless shelters, and prisons. Measures to limit such transmission include respiratory isolation of persons with suspected tuberculosis until they are proven to be noninfectious (i.e., by sputumAFBsmear negativity), proper ventilation in rooms of patients with infectious tuberculosis, use of ultraviolet lights in areas of increased risk of tuberculosis transmission, and periodic screening of personnel who may come into contact with known or unsuspected cases of tuberculosis. In the past, radiographic surveys, especially those conducted with portable equipment and miniature films, were advocated for case finding. Today, however, the prevalence of tuberculosis in industrialized countries is sufficiently low that "mass miniature radiography" is not

cost-effective. As mentioned above, current recommendations for the prevention and treatment of tuberculosis in HIV-infected individuals have been published by theCDC.

In high-prevalence countries, tuberculosis control programs should be based on the following key elements: (1) case detection through microscopic examination of sputum from patients who present to health care facilities with cough of>3 weeks' duration; (2) administration of standard short-course chemotherapy to all sputum smear-positive patients, with direct observation of drug ingestion; (3) establishment and maintenance of a system of regular drug supply; and (4) establishment and maintenance of an effective surveillance and treatment-monitoring system allowing an analysis of treatment outcomes (e.g., cure, completion of treatment without bacteriologic proof of cure, death, treatment failure, and default) in all cases registered.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 170. LEPROSY (HANSEN'S DISEASE) - *Robert H. Gelber*

Leprosy, first described in ancient Indian texts from the sixth century B.C., is a nonfatal, chronic infectious disease caused by *Mycobacterium leprae*, whose clinical manifestations are largely confined to the skin, peripheral nervous system, upper respiratory tract, eyes, and testes. The unique tropism of *M. leprae* for peripheral nerves (from large nerve trunks to microscopic dermal nerves) and certain immunologically mediated reactional states are the major causes of morbidity in leprosy. The propensity of the disease, when untreated, to result in certain characteristic deformities and the recognition in most cultures that the disease is communicable from person to person have resulted historically in a profound social stigma. Today, with early diagnosis and the institution of appropriate and effective antimicrobial therapy, patients can lead productive lives in the community, and deformities and other visible manifestations can largely be prevented.

### ETIOLOGY

*M. leprae* is an obligate intracellular bacillus (0.3 to 1 um wide and 1 to 8 um long) that is acid-fast, indistinguishable microscopically from other mycobacteria, ideally detected in tissue sections by a modified Fite stain, and without demonstrable strain variability. *M. leprae* produces no known toxins and is well adapted to penetrate and reside within macrophages, yet it may survive outside the body for 7 to 10 days. In untreated patients, only ~1% of *M. leprae* organisms are viable. The morphologic index, a measure of the number of acid-fast bacilli (AFB) in skin scrapings that stain uniformly bright, correlates with viability. The bacteriologic index, a logarithmic-scaled measure of the density of *M. leprae* in the dermis, may be as high as 4+ to 6+ in untreated patients, falling by one unit per year during effective therapy; the rate of fall is independent of the relative potency of effective antimicrobial therapy. A rising bacteriologic or morphologic index suggests relapse and perhaps -- if the patient is being treated -- drug resistance; the latter possibility can be confirmed or excluded in the mouse model.

The genome of *M. leprae* is only 3 million base pairs, two-thirds as large as that of *M. tuberculosis*. The bacterium's complex cell wall has a peptidoglycan backbone, which is linked to arabinogalactan and mycolic acids. Lipoarabinomannan is a key component of the cell membrane, and the outer capsule contains large amounts of an *M. leprae*-specific phenolic glycolipid (PGL-1), which is detected in serologic tests. In addition, highly conserved, usually immunogenic heat-shock proteins containing *M. leprae*-specific and mycobacterial cross-reactive epitopes are found in the cytoplasm and cell wall.

Among the mycobacteria, *M. leprae* is unique in exhibiting dopa oxidase activity and an acid-fastness that is pyridine-extractable. Although it was the first bacterium to be etiologically associated with human disease, *M. leprae* remains one of the few bacterial species that still has not been cultivated on artificial medium or tissue culture. The multiplication of *M. leprae* in mouse footpads (albeit limited, with a doubling time of ~2 weeks) has provided a means to evaluate antimicrobial agents, monitor clinical trials, and screen vaccines. *M. leprae* grows best in cooler tissues (the skin, peripheral nerves, anterior chamber of the eye, upper respiratory tract, and testes), sparing warmer areas of the skin (the axilla, groin, scalp, and midline of the back).

## EPIDEMIOLOGY

**Demographics** Leprosy is almost exclusively a disease of the developing world, affecting areas of Asia, Africa, Latin America, and the Pacific. While Africa has the highest disease prevalence, Asia has the most cases. More than 80% of the world's cases occur in a few countries: India, China, Myanmar, Indonesia, Brazil, and Nigeria. Within endemic locales, the distribution of leprosy is quite uneven, with areas of high prevalence bordering on areas with little or no disease. In Brazil the majority of cases occur in the Amazon basin, while in Mexico leprosy is mostly confined to western states. Except as imported cases, leprosy is largely absent from the United States, Canada, and northwestern Europe. In the United States, ~4000 persons have leprosy and 100 to 200 new cases are reported annually, most of them in California, Texas, New York, and Hawaii among immigrants from Mexico, Southeast Asia, the Philippines, and the Caribbean.

The global prevalence of leprosy is difficult to assess, given that many of the locales with high prevalence lack a significant medical or public health infrastructure. Estimates range from 1.5 to 8 million affected individuals. The lower estimate includes only persons who have not completed chemotherapy, excluding those who may be physically or psychologically damaged from leprosy and who may yet relapse or develop certain immune-mediated reactions; the higher figure includes patients whose infections probably are already cured and many who have no leprosy-related deformity or disability. Although the figures on the worldwide prevalence of leprosy are debatable, it is generally agreed that the annual incidence of new cases is stable and approximates 600,000.

Leprosy is associated with poverty and rural residence. It appears not to be associated with AIDS, perhaps because of leprosy's long incubation period. Most people appear to be naturally immune to leprosy and do not develop disease manifestations following exposure. The time of peak onset is in the second and third decades of life. The most severe form, lepromatous leprosy, is twice as common among men as among women and is rarely encountered in children. The frequency of the polar forms of leprosy (see "Clinical, Histologic, and Immunologic Spectrum," below) in different countries varies widely and may in part be genetically determined; certain HLA associations are known for both lepromatous and tuberculoid leprosy (see below). In India and Africa, 90% of cases are tuberculoid; in Southeast Asia, 50% are lepromatous and 50% tuberculoid; and in Mexico, 90% are lepromatous.

**Transmission** *M. leprae* causes disease primarily in humans. However, in Texas and Louisiana, 15% of nine-banded armadillos are infected, and armadillo contact occasionally results in human disease. Following intravenous experimental inoculation of *M. leprae*, 60% of armadillos develop a heavy disseminated infection of the liver, spleen, lymph nodes, and skin; these experimental animals have been the source of vast quantities of *M. leprae* organisms for laboratory and clinical research.

The route of transmission of leprosy remains uncertain and may be multiple; nasal droplet infection, contact with infected soil, and even insect vectors have been considered the prime candidates. Aerosolized *M. leprae* can cause infection in

immunosuppressed mice, and a sneeze from an untreated lepromatous patient may contain>$10^{10}$AFB. Furthermore, both IgA antibody to *M. leprae* and genes of *M. leprae* -- demonstrable by polymerase chain reaction (PCR) -- have been found in the nose of individuals without signs of leprosy from endemic areas and in 19% of occupational contacts of lepromatous patients.

Several lines of evidence implicate soil transmission of leprosy. (1) In endemic countries such as India, leprosy is primarily a rural and not an urban disease. (2) *M. leprae* products have been demonstrated to be resident in soil in endemic locales. (3) Direct dermal inoculation (e.g., during tattooing) may transmit *M. leprae*, and common sites of leprosy in children are the buttocks and thighs, suggesting that microinoculation of infected soil may transmit the disease.

Evidence for insect vectors of leprosy includes the demonstration that bedbugs and mosquitoes in the vicinity of leprosaria regularly harbor *M. leprae* and that experimentally infected mosquitoes can transmit infection to mice. Skin-to-skin contact is generally not considered an important route of transmission.

In endemic countries, ~50% of leprosy patients have a history of intimate contact with an infected person (often a household member), while, for unknown reasons, leprosy patients in nonendemic locales can identify such contact only 10% of the time. Moreover, household contact with an infected lepromatous case carries an eventual risk of disease acquisition of ~10% in endemic areas as opposed to only 1% in nonendemic locales. Contact with a tuberculoid case carries a very low risk. Physicians and nurses caring for leprosy patients and the co-workers of these patients are not at risk for leprosy.

## CLINICAL, HISTOLOGIC, AND IMMUNOLOGIC SPECTRUM

The incubation period prior to manifestation of clinical disease can vary between 2 and 40 years, although it is generally 5 to 7 years in duration. Leprosy presents as a spectrum of clinical manifestations that have pathologic and immunologic counterparts. The spectrum from polar tuberculoid (TT) to borderline tuberculoid (BT) to borderline lepromatous (BL) to polar lepromatous (LL) disease is associated with an evolution from localized to more generalized disease manifestations, an increasing bacterial load, and loss of *M. leprae*-specific cellular immunity. Where a patient presents on the clinical spectrum largely determines prognosis, complications, reactional states, and the intensity of antimicrobial therapy required.

**Tuberculoid Leprosy** At the less severe end of the spectrum is tuberculoid leprosy, which encompasses TT and BT disease. In general, these forms of leprosy result in symptoms confined to the skin and peripheral nerves. The initial lesion of tuberculoid leprosy is often a hypopigmented macule that is sharply demarcated and hypesthetic. Later, the lesions enlarge by peripheral spread, and the margins become elevated and circinate or gyrate. The central area in turn becomes atrophic and depressed. Fully developed lesions are densely anesthetic and devoid of the normal skin organs (sweat glands and hair follicles). Patients eventually have one or more asymmetrically distributed, hypopigmented, anesthetic, nonpruritic, well-defined macules, often with an erythematous or raised border (Fig. 170-1;Fig. 170-CD1). Skin lesions of tuberculoid

leprosy vary in diameter from one to several centimeters and are often dry, scaly, and anhidrotic. Tuberculoid leprosy patients may also have asymmetric enlargement of one or a few peripheral nerves. Indeed, leprosy and certain rare hereditary neuropathies are the only human diseases associated with peripheral-nerve enlargement. Although any peripheral nerve may be enlarged (including small digital and supraclavicular nerves), those most commonly affected are the ulnar, posterior auricular, peroneal, and posttibial nerves, with associated hypesthesia and myopathy. At times, tuberculoid leprosy may present with only nerve-trunk involvement with no skin lesions; in such cases it is termed *neural leprosy*. TT leprosy may resolve spontaneously and is not associated with lepra reactions (see "Reactional States," below). BT leprosy does not heal spontaneously and may be associated with type 1 lepra reactions but not with erythema nodosum leprosum (ENL). TT leprosy is the most common form of the disease encountered in India and Africa but is virtually absent in Southeast Asia, where BT leprosy is frequent.

In TT leprosy the epidermis may be involved histologically, while in all other forms of leprosy the epidermis and the superficial dermis are spared, with pathology confined to the deeper dermis. On hematoxylin and eosin staining, TT and BT lesions appear as well-defined noncaseating granulomas with many lymphocytes and Langhans' giant cells. In tuberculoid leprosy, T cells breach the perineurium, and destruction of Schwann cells and axons may be evident, resulting in fibrosis of the epineurium, replacement of the endoneurium with epithelial granulomas, and occasionally caseous necrosis.AFB are generally absent or few in number. Such invasion and destruction of nerves in the dermis by T cells are pathognomonic for leprosy.

Circulating lymphocytes from patients with tuberculoid leprosy readily recognize *M. leprae* and its constituent proteins, and patients have positive lepromin skin tests (see "Diagnosis" below). In tuberculoid leprosy tissue, there is a 2:1 predominance of helper CD4+ over CD8+ T lymphocytes. Tuberculoid tissues are rich in the mRNAs of the proinflammatory $T_H1$ family of cytokines: interleukin (IL) 2, interferon g(IFN-g), and IL-12; in contrast, IL-4, IL-5, and IL-10 mRNAs are scarce.

**Lepromatous Leprosy** At the more severe end of the leprosy spectrum is lepromatous disease, which encompasses the LL and BL forms. The initial skin lesions of lepromatous leprosy are skin-colored or slightly erythematous papules or nodules. In time, individual lesions grow in diameter up to 2 cm; new papules and nodules then appear and may coalesce. Patients later present with symmetrically distributed skin nodules, raised plaques, or diffuse dermal infiltration (Fig. 170-CD2), which, when on the face, results in leonine facies. Late manifestations include loss of eyebrows (initially the lateral margins only; see Plate IID-56) and eyelashes, pendulous earlobes, and dry scaling skin, particularly on the feet. Almost exclusively found in western Mexico and the Caribbean is a form of lepromatous leprosy without visible skin lesions but with diffuse dermal infiltration and a demonstrably thickened dermis, termed *diffuse lepromatosis*. In lepromatous leprosy, nerve enlargement and damage tend to be symmetric, result from actual bacillary invasion, and are more insidious but ultimately more extensive than in tuberculoid leprosy. Patients with LL leprosy have symmetric acral distal peripheral neuropathy and a tendency toward symmetric nerve-trunk enlargement. They may also have signs and symptoms related to involvement of the upper respiratory tract, the anterior chamber of the eye, and the testes.

Dermatopathology in lepromatous leprosy is confined to the dermis and particularly affects the dermal appendages. Histologically, the dermis characteristically contains highly vacuolated cells (*foam cells*) otherwise found only in certain lipid-storage disorders. Indeed, on fat staining, these vacuoles are highly positive and are seen to include large amounts of *M. leprae*-associated cell wall lipids and the *M. leprae*-specificPGL-1. The dermis in lepromatous leprosy contains few lymphocytes and giant cells, and granulomas are absent. In LL leprosy, bacilli are numerous in the skin (as many as $10^9$/g), where they are often found in large clumps (*globi*), and in peripheral nerves, where they initially invade Schwann cells, resulting in foamy degenerative myelination and axonal degeneration and later in Wallerian degeneration. In addition, bacilli are plentiful in circulating blood and in all organ systems except the lungs and the central nervous system. Nevertheless, patients are afebrile, and there is no evidence of major organ system dysfunction. The dermis contains more lymphocytes and fewerAFB and exhibits less vacuolization in BL than in LL leprosy.

In untreated LL patients, lymphocytes regularly fail to recognize either *M. leprae* or its protein constituents, and lepromin skin tests are negative (see "Diagnosis," below). This loss of protective cellular immunity appears to be antigen-specific, as patients are not unusually susceptible to opportunistic infections, cancer, or AIDS and maintain delayed-type hypersensitivity to *Candida*, *Trichophyton*, mumps, tetanus toxoid, and even purified protein derivative of tuberculin. At times, *M. leprae*-specific anergy is reversible with effective chemotherapy. In LL tissues, there is a 2:1 ratio of CD8+ to CD4+ T lymphocytes. LL tissues demonstrate a $T_H2$ cytokine profile, being rich in mRNAs forIL-4, IL-5, and IL-10 and poor in those for IL-2,IFN-g, and IL-12. It appears that cytokines mediate a protective tissue response in leprosy, as injection of IFN-g or IL-2 into lepromatous lesions causes a loss ofAFB and histopathologic conversion toward a tuberculoid pattern. Macrophages of lepromatous leprosy patients appear to be functionally intact; circulating monocytes exhibit normal microbicidal function and responsiveness to IFN-g.

LL and BL patients may develop type 2 lepra reactions (ENL; see "Reactional States," below), while BL patients (but not LL patients) can have type 1 lepra reactions.

**Reactional States** Lepra reactions comprise several common immunologically mediated inflammatory states that cause considerable morbidity. Some of these reactions precede diagnosis and the institution of effective antimicrobial therapy. Indeed, these reactions may precipitate presentation for medical attention and diagnosis; others occur after the initiation of appropriate chemotherapy. In the latter circumstances, patients often lose confidence in conventional therapy, perceiving that their leprosy is worsening. Only by warning patients of the potential for these reactions and describing their manifestations can physicians treating leprosy patients ensure continued credibility.

*Type 1 Lepra Reactions (Downgrading and Reversal Reactions)* These reactions occur in almost half of patients with borderline forms of leprosy but not in patients with polar disease. Manifestations include classic signs of inflammation within previously involved macules, papules, and plaques and, on occasion, the appearance of new skin lesions, neuritis, and (less commonly) fever -- generally low-grade. The nerve trunk most

commonly involved in this process is the ulnar nerve at the elbow, which may be painful and exquisitely tender. If patients with affected nerves are not treated promptly with glucocorticoids (see below), irreversible nerve damage may result in as little as 24 h. The most dramatic manifestation is footdrop, which occurs when the peroneal nerve is involved.

When type 1 lepra reactions precede the initiation of appropriate antimicrobial therapy, they are termed *downgrading reactions*, and the case becomes histologically more lepromatous; when they occur after the initiation of therapy, they are termed *reversal reactions*, and the case becomes more tuberculoid. Reversal reactions often occur in the first months or years after the initiation of therapy but may also develop several years thereafter.

Edema is the most characteristic microscopic feature of type 1 lepra lesions, whose diagnosis is primarily clinical. Reversal reactions are typified by a $T_H1$ cytokine profile, with an influx of CD4+ helper cells and increased levels ofIFN-gandIL-2. In addition, type 1 reactions are associated with large numbers of T cells bearinggg/¶receptors -- a unique feature of leprosy.

Type 1 lepra reactions are best treated with glucocorticoids (e.g., prednisone, initially at doses of 40 to 60 mg/d). As the inflammation subsides, the glucocorticoid dose can be tapered, but steroid therapy must be continued for at least 3 months lest recurrence supervene. Because of the myriad toxicities of prolonged glucocorticoid therapy, the indications for its initiation are strictly limited to lesions whose intense inflammation poses a threat of ulceration; lesions at cosmetically important sites, such as the face; and the presence of neuritis. Mild to moderate lepra reactions that do not meet these criteria should be tolerated and glucocorticoid treatment withheld. Thalidomide is ineffective against type 1 lepra reactions; clofazimine (200 to 300 mg/d) is of questionable benefit but in any event is far less efficacious than glucocorticoids.

*Type 2 Lepra Reactions (ENL)* ENLoccurs exclusively in patients near the lepromatous end of the leprosy spectrum, affecting nearly 50% of this group. Although ENL may precede leprosy diagnosis and initiation of therapy -- sometimes, in fact, prompting the diagnosis -- in 90% of cases it follows the institution of chemotherapy, generally within 2 years. The most common features of ENL are crops of painful erythematous papules that resolve spontaneously in a few days to a week but may recur; malaise; and fever that can be profound. However, patients may also experience symptoms of neuritis, lymphadenitis, uveitis, orchitis, and glomerulonephritis and may develop anemia, leukocytosis, and abnormal liver function tests, particularly increased aminotransferase levels. Individual patients may have either a single bout of ENL or chronic recurrent manifestations. Bouts may be either mild or severe and generalized; in rare instances, ENL results in death.

Skin biopsy ofENLpapules reveals vasculitis or panniculitis, sometimes with many lymphocytes but characteristically with polymorphonuclear leukocytes as well.

Elevated levels of circulating tumor necrosis factor (TNF) have been demonstrated inENL; thus TNF may play a central role in the pathobiology of this syndrome. ENL is thought to be a consequence of immune complex deposition, given its $T_H2$ cytokine

profile and its high levels ofIL-6 and IL-8. However, in ENL tissue, the presence of HLA Dr framework antigen of epidermal cells -- considered a marker for a delayed-type hypersensitivity response -- and evidence for higher levels of IL-2 andIFN-gthan are usually seen in polar lepromatous disease suggest an alternative mechanism.

Treatment must be individualized. IfENL is mild (i.e., without fever or other organ involvement, with occasional crops of only a few skin papules), it may be treated with antipyretics alone. However, in cases with many skin lesions, fever, malaise, and other tissue involvement, brief courses (1 to 2 weeks) of glucocorticoids (initially 40 to 60 mg/d) are often effective. With or without therapy, individual inflamed papules last for£1 week. Successful therapy is defined by the cessation of skin lesion development and the disappearance of other systemic signs and symptoms. If, despite two courses of glucocorticoid therapy, ENL appears to be recurring and persisting, treatment with thalidomide (100 to 300 mg nightly) should be initiated, with the dose depending on the initial severity of the reaction. Because even a single dose of thalidomide administered early in pregnancy may result in severe birth defects, including phocomelia, the use of this drug in the United States for the treatment of fertile females is tightly regulated and requires informed consent, prior pregnancy testing, and maintenance of birth control measures. Although the mechanism of thalidomide's dramatic action against ENL is not entirely clear, the drug's efficacy is probably attributable to its reduction ofTNFlevels and IgM synthesis and its slowing of polymorphonuclear leukocyte migration. After the reaction is controlled, lower doses of thalidomide (50 to 200 mg nightly) are effective in preventing relapses of ENL. Clofazimine in high doses (300 mg nightly) has some efficacy against ENL, but its use permits only a modest reduction of the glucocorticoid dose necessary for ENL control.

*Lucio's Phenomenon* This unusual reaction is seen exclusively in patients from the Caribbean and Mexico who have the diffuse lepromatosis form of lepromatous leprosy, most often those who are untreated. Patients with this reaction develop recurrent crops of large, sharply marginated, ulcerative lesions -- particularly on the lower extremities -- that may be generalized and, when so, are frequently fatal as a result of secondary infection and consequent septic bacteremia. Histologically, the lesions are characterized by ischemic necrosis of the epidermis and superficial dermis, heavy parasitism of endothelial cells withAFB, and endothelial proliferation and thrombus formation in the larger vessels of the deeper dermis. LikeENL, the Lucio reaction is probably mediated by the immune complex. Neither glucocorticoids nor thalidomide is effective against this syndrome. Optimal wound care and therapy for bacteremia are indicated. Ulcers tend to be chronic and heal poorly. In severe cases, exchange transfusion may prove useful.

*Nerve Abscesses* Patients with various forms of leprosy, but particularly those with the BT form, may develop abscesses of nerves (most commonly the ulnar) with an adjacent cellulitic appearance of the skin. In such conditions, the affected nerve is swollen and exquisitely tender. Although glucocorticoids may reduce signs of inflammation, rapid surgical decompression is necessary to prevent irreversible sequelae.

**Complications**

*The Extremities* Complications of the extremities in leprosy patients are primarily a consequence of neuropathy leading to insensitivity and myopathy. Insensitivity affects

fine touch, pain, and heat receptors but generally spares position and vibration appreciation. The most commonly affected nerve trunk is the ulnar nerve at the elbow, whose involvement results in clawing of the fourth and fifth fingers, loss of dorsal interosseous musculature in the affected hand, and loss of sensation in these distributions. Median nerve involvement in leprosy impairs thumb opposition and grasp, while radial nerve dysfunction, though rare in leprosy, leads to wristdrop. Tendon transfers can restore hand function but should not be performed until 6 months after the initiation of antimicrobial therapy and the conclusion of episodes of acute neuritis.

Plantar ulceration, particularly at the metatarsal heads, is probably the most frequent complication of leprous neuropathy. Plantar ulcers may become secondarily infected and lead to adjacent cellulitis and osteomyelitis. Because of the importance and critical integrity of the normal plantar fat pad, recurrent ulceration is unfortunately common once initial ulceration has occurred and the pad has been replaced by thin and less resilient fibrous scar tissue. The treatment of plantar ulceration includes debridement of devitalized and undermined tissue; discontinuation of weight-bearing, which may be accomplished by means of a total-contact cast or bed rest; and vigorous treatment of secondary infection, which most commonly is due to *Staphylococcus aureus*. Once healing takes place, walking must be limited, especially during the first week, with slow and progressive increases thereafter. Extra-depth shoes or individually fitted shoes with specially molded inserts are required to prevent recurrence.

Peroneal nerve palsies may result from leprosy itself or from one of its reactional states; the consequence is partial or complete footdrop, which causes an uneven distribution of weight on the plantar surface and hence a predilection to ulceration. Simple nonmetallic braces within the shoe may be useful, while tendon transfers can actually correct footdrop. Although uncommon, Charcot's joints, particularly of the foot and ankle, may result from leprosy.

The loss of distal digits in leprosy is a consequence of insensitivity, trauma, secondary infection, and -- in lepromatous patients -- a poorly understood and sometimes profound osteolytic process. Conscientious protection of the extremities during cooking and work and the early institution of therapy have substantially reduced the frequency and severity of distal digit loss in recent times.

*The Nose* In lepromatous leprosy, bacillary invasion of the nasal mucosa can result in chronic nasal congestion and epistaxis. Saline nosedrops may relieve these symptoms. Long-untreated LL leprosy may further result in destruction of the nasal cartilage, with consequent saddle-nose deformity or anosmia (more common in the preantibiotic era than at present). Nasal reconstructive procedures can ameliorate significant cosmetic defects.

*The Eye* Owing to cranial nerve palsies, lagophthalmus and corneal insensitivity may complicate leprosy, resulting in trauma, secondary infection, and (without treatment) corneal ulcerations and opacities. For patients with these conditions, eyedrops during the day and ointments at night provide some protection from such consequences. Furthermore, in LL leprosy, the anterior chamber of the eye is invaded by bacilli, andENL may result in uveitis, with consequent cataracts and glaucoma. Thus leprosy is a major cause of blindness in the developing world. Slit-lamp evaluation of LL patients

often reveals "corneal beading," representing globi of *M. leprae*.

*The testes M. leprae* invades the testes, whileENL may cause orchitis. Thus males with lepromatous leprosy often manifest mild to severe testicular dysfunction, with an elevation of luteinizing and follicle-stimulating hormones, decreased testosterone, and aspermia or hypospermia in 85% of LL patients but in only 25% of BL patients. LL patients may become impotent and infertile. Impotence is sometimes responsive to testosterone replacement.

*Amyloidosis* Secondary amyloidosis is a complication of LL leprosy andENL that is encountered infrequently in the antibiotic era. This complication may result in abnormalities of hepatic and particularly renal function.

**DIAGNOSIS**

Leprosy most commonly presents with both characteristic skin lesions and skin histopathology. Thus the disease should be suspected when a patient from an endemic area has suggestive skin lesions or peripheral neuropathy; the diagnosis should be confirmed by histopathology. In tuberculoid leprosy, lesional areas -- preferably the advancing edge -- must be biopsied because normal-appearing skin does not have pathologic features. In lepromatous leprosy, nodules, plaques, and indurated areas are optimal biopsy sites, but biopsies of normal-appearing skin are also generally diagnostic. Lepromatous leprosy is associated with diffuse hyperglobulinemia, which may result in false-positive serologic tests (e.g., VDRL, RA, ANA) and therefore can cause diagnostic confusion. On occasion, tuberculoid lesions may not (1) appear typical, (2) be hypesthetic, and (3) contain granulomas but only nonspecific lymphocytic infiltrates. In such instances, two of these three characteristics are considered sufficient for a diagnosis. It is preferable to overdiagnose leprosy rather than to allow a patient to remain untreated.

IgM antibodies toPGL-1are found in 95% of untreated lepromatous leprosy patients; the titer decreases with effective therapy. However, in tuberculoid leprosy -- the form of disease most often associated with diagnostic uncertainty owing to the absence ofAFB -- patients have significant antibodies to PGL-1 only 60% of the time; moreover, in endemic locales, exposed individuals without clinical leprosy may harbor antibodies to PGL-1. Thus PGL-1 serology is of little diagnostic utility in tuberculoid leprosy.
Heat-killed *M. leprae* (lepromin) has been used as a skin test reagent. It generally elicits a reaction in tuberculoid leprosy patients, may do so in individuals without leprosy, and gives negative results in lepromatous leprosy patients; consequently, it is likewise of little diagnostic value. Unfortunately,PCR of skin for *M. leprae*, although positive in LL and BL leprosy, yields negative results in 50% of tuberculoid leprosy cases, again offering little diagnostic assistance.

Included in the differential diagnosis of lesions that resemble leprosy are sarcoidosis, leishmaniasis, lupus vulgaris, lymphoma, syphilis, yaws, granuloma annulare, and various other disorders causing hypopigmentation. Sarcoidosis may result in perineural inflammation, but actual granuloma formation within dermal nerves is pathognomonic for leprosy. In lepromatous leprosy, sputum specimens may be loaded withAFB -- a finding that can be inappropriately interpreted as representing pulmonary tuberculosis.

## TREATMENT

**Active Agents** Established agents used to treat leprosy include dapsone (50 to 100 mg/d), clofazimine (50 to 100 mg/d, 100 mg three times weekly, or 300 mg monthly), and rifampin (600 mg daily or monthly). Of these drugs, only rifampin is bactericidal. The sulfones (folate antagonists), the foremost of which is dapsone, were the first antimicrobials found to be effective for the treatment of leprosy and are still the mainstay of therapy. With sulfone treatment, skin lesions resolve and numbers of viable bacilli in the skin are reduced. Although primarily bacteriostatic, dapsone monotherapy results in only a 10% resistance-related relapse rate; after ³18 years of therapy and subsequent discontinuation, only another 10% of patients relapse, developing new, usually asymptomatic, shiny, "histoid" nodules. Dapsone is generally safe and inexpensive. Individuals with glucose-6-phosphate dehydrogenase deficiency who are treated with dapsone may develop severe hemolysis; those without this deficiency also have reduced red cell survival and a hemoglobin decrease averaging 1 g/dL. Dapsone's usefulness is limited occasionally by allergic dermatitis and rarely by the sulfone syndrome (including high fever, anemia, exfoliative dermatitis, and a mononucleosis-type blood picture). It must be remembered that rifampin induces microsomal enzymes, necessitating increased doses of medications such as glucocorticoids and oral birth control regimens. Clofazimine is often cosmetically unacceptable to light-skinned leprosy patients because it causes a red-black skin discoloration that accumulates, particularly in lesional areas, and makes the patient's diagnosis obvious to members of the community.

Other antimicrobial agents active against *M. leprae* in animal models and at the usual daily doses used in clinical trials include ethionamide/prothionamide; the aminoglycosides streptomycin, kanamycin, and amikacin (but not gentamicin or tobramycin); minocycline; clarithromycin; and several fluoroquinolones, particularly ofloxacin. Next to rifampin, minocycline, clarithromycin, and ofloxacin appear to be most bactericidal for *M. leprae*, but these drugs have not been used extensively in leprosy control programs.

**Choice of Regimens** Antimicrobial therapy for leprosy must be individualized, depending on the clinical/pathologic form of the disease encountered. Tuberculoid leprosy, which is associated with a low bacterial burden and a protective cellular immune response, is the easier form to treat and can be reliably cured with a finite course of chemotherapy. In contrast, lepromatous leprosy may have a higher bacillary load than any other human bacterial disease, and the absence of a salutary T cell repertoire requires prolonged or even lifelong chemotherapy. Hence, careful classification of disease prior to therapy is important. In developed countries, clinical experience with leprosy classification is limited; fortunately, however, the resources needed for skin biopsy are highly accessible and pathologic interpretation is readily available. In developing countries, clinical expertise is greater, but it may now be waning as the care of leprosy patients is integrated into general health services. In addition, access to dermatopathology services is often limited. In such instances, skin smears may prove useful, but in many locales access to the resources needed for their preparation and interpretation may also be unavailable.

A reasoned approach to the treatment of leprosy is confounded by these and several other issues:

1. Even without therapy, TT leprosy may heal spontaneously, and prolonged dapsone monotherapy (even for LL leprosy) is generally curative in 80% of cases.

2. In tuberculoid disease, there are often no bacilli found in the skin prior to therapy, and thus there is no objective measure of therapeutic success. Furthermore, despite adequate treatment, TT and particularly BT lesions often resolve little or incompletely, while relapse and late type 1 lepra reactions can be difficult to distinguish.

3. LL leprosy patients commonly harbor viable persistent *M. leprae* organisms after prolonged intensive therapy; the propensity of these organisms to initiate clinical relapse is unclear. Because relapse in LL patients after discontinuation of rifampin-containing regimens usually begins only after 7 to 10 years, follow-up over the very long term is necessary to assess ultimate clinical outcomes.

4. Even though primary dapsone resistance is exceedingly rare and multidrug therapy is generally recommended (at least for lepromatous leprosy), there is a paucity of information from experimental animals and clinical trials on the optimal combination of antimicrobials, dosing schedule, or duration of therapy.

In 1982, the World Health Organization (WHO) made recommendations for "the chemotherapy of leprosy for control programs." These recommendations came on the heels of the demonstration of the relative success of long-term dapsone monotherapy and in the context of concerns about dapsone resistance. Other complicating considerations included the limited resources available for leprosy care in the very areas where it is most prevalent and the frustration and discouragement of patients and program managers with the previous requirement for lifelong therapy for many leprosy patients. The WHO delineated for the first time a finite duration of therapy for all forms of leprosy, and -- given the prohibitive cost of daily rifampin treatment in developing countries -- encouraged the monthly administration of this agent as part of a multidrug regimen.

Over the ensuing years, theseWHOrecommendations have been broadly implemented, and the duration of therapy required, particularly for lepromatous leprosy, has been progressively shortened. For treatment purposes, the WHO classifies patients as paucibacillary and multibacillary. Previously, patients without demonstrableAFB in the dermis were classified as paucibacillary and those with AFB as multibacillary. Currently, owing to the perceived unreliability of skin smears in the field, patients are classified as multibacillary if they have five or more skin lesions and as paucibacillary if they have fewer than five skin lesions. The WHO recommends that paucibacillary adults be treated with 100 mg of dapsone daily and 600 mg of rifampin monthly (supervised) for 6 months (Table 170-1). Multibacillary adults should be treated with 100 mg of dapsone plus 50 mg of clofazimine daily (unsupervised) and with 600 mg of rifampin plus 300 mg of clofazimine monthly (supervised). Originally, the WHO recommended that lepromatous patients be treated for 2 years or until smears became negative (generally in ~5 years); subsequently, the acceptable course was reduced to 1 year -- a change that remains controversial in the absence of clinical trials.

Several factors, including an improved economic climate, the high relapse rates (20 to 40%, depending on the initial bacterial burden) among patients with lepromatous leprosy afterWHO-recommended treatment, and the demonstrable lesional activity in fully half of tuberculoid leprosy patients after the completion of therapy, have caused many authorities to question the WHO recommendations and to favor a more intensive approach. This approach (Table 170-1) calls for tuberculoid leprosy to be treated with dapsone (100 mg/d) for 5 years and for lepromatous leprosy to be treated with rifampin (600 mg/d) for 3 years and with dapsone (100 mg/d) throughout life.

On effective antimicrobial therapy, new skin lesions and signs and symptoms of peripheral neuropathy cease appearing. Nodules and plaques of lepromatous leprosy noticeably flatten in 1 to 2 months and resolve in 1 or a few years, while tuberculoid skin lesions may disappear, improve, or remain relatively unchanged. Though the peripheral neuropathy of leprosy may improve somewhat in the first few months of therapy, rarely is it significantly ameliorated by treatment.

## PREVENTION AND CONTROL

Vaccination at birth with bacille Calmette-Guerin (BCG) has proved variably effective in preventing leprosy, ranging from totally ineffective to 80% efficacious. The addition of heat-killed *M. leprae* to BCG does not increase vaccine efficacy. Because whole mycobacteria contain large amounts of lipids and carbohydrates that have proven in vitro to be immunosuppressive for lymphocytes and macrophages, *M. leprae* proteins may prove to be superior vaccines. Data from a mouse model support this possibility. Chemoprophylaxis with dapsone may reduce the number of cases of tuberculoid leprosy but not of lepromatous leprosy and hence is not recommended, even for household contacts. Because leprosy transmission appears to require close prolonged household contact, hospitalized patients need not be isolated.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 171. INFECTIONS DUE TO NONTUBERCULOUS MYCOBACTERIA - *Bernard Hirschel*

Mycobacteria are slightly curved or straight, rod-shaped or coccoid bacilli traditionally identified by the property of acid-fastness: once stained, the organisms are not easily decolorized, even with acid-alcohol, because of the composition of their cell walls. The genetic relation of mycobacteria with one another is evidenced by their ribosomal RNA sequence homology, which can be used for diagnostic purposes.

Because of the overwhelming clinical importance of tuberculosis, mycobacteriologists have distinguished the *Mycobacterium tuberculosis* complex (consisting of *M. tuberculosis*, *M. bovis*, and *M. africanum*) from all other mycobacteria. Except for *M. leprae* (Chap. 170), the other mycobacteria are referred to as atypical mycobacteria, mycobacteria other than tuberculosis (MOTT), or nontuberculous mycobacteria (NTM). The most clinically important NTM are listed and described in Table 171-1. The isolation of NTM -- or the lack thereof -- from an individual patient or laboratory specimen must be interpreted with the following facts in mind:

1. SomeNTMrequire special media and/or growth conditions. The laboratory must be alerted and cultures for acid-fast bacilli requested if the diagnosis of these infections is not to be missed.

2. NTM grow slowly. Even the so-called rapid growers take 3 to 7 days to form visible colonies on solid media, whereas slow-growing mycobacteria take weeks or do not grow at all on artificial media.

3. The slow growth of mycobacteria complicates antibiotic susceptibility testing. During prolonged incubation, antibiotics may be degraded and disappear from the culture medium. Long delays reduce the clinical usefulness of whatever results are eventually obtained.

4. Data on in vitro susceptibility correlate poorly with clinical results. For example, clarithromycin and azithromycin are highly and variably concentrated in tissues; consequently, the concentrations necessary for determining resistance are difficult to establish in vitro. Sensitivity testing, based on achievable serum levels, would have predicted that these drugs would have little efficacy in vivo; in fact, the opposite is true, both in animal models and in humans.

5. In contrast to *M. tuberculosis*,NTM are ubiquitous in the environment. Therefore, isolation of NTM from a site that is not normally sterile (such as sputum, urine, skin, or feces) does not constitute proof of disease. In Switzerland between 1983 and 1988, for example, only 23 of 513 HIV-negative patients with NTM isolates had clinically significant disease. Clusters of unusual isolates are more likely to suggest contamination -- e.g., from tap water or bronchoscopy equipment -- than to represent an epidemic of disease.

The original method for the classification ofNTM, developed between 1950 and 1980, depends on speed of growth, morphology, and pigmentation of colonies on solid media as well as biochemical reactions. Although reliable and inexpensive, these procedures

take a long time; a period of 12 weeks is often required for definitive identification. Of course, such delayed results are of little use in the care of patients.

The isolation ofNTM from blood cultures requires the use of a special medium for lysis-centrifugation or broth culture. The lysis-centrifugation method (lysis of blood cells followed by centrifugation and plating of the pellet with the bacteria on solid medium) permits quantification of bacteremia; however, some mycobacteria (e.g., *M. genavense*) do not grow well on solid medium and will not be detected by this method. Culture in liquid broth, such as that used in the radiometric Bactec system, shortens the time needed to identify a positive culture but also precludes the study of colonial morphology and pigmentation. Molecular probes are now used for rapid identification of the most important species (*M. avium*, *M. intracellulare*, *M. gordonae*, *M. kansasii*, and the *M. tuberculosis* complex) in a positive culture; a color is produced upon hybridization of the probe to specific sequences of the mycobacterial ribosome.

Twenty years ago, the field of mycobacteriology was something of a backwater. Tuberculosis was incorrectly perceived as a disappearing problem, andNTM were causing only rare and chronic diseases. AIDS, however, has brought mycobacterial infections to the forefront of clinical medicine once more. HIV and *M. tuberculosis* make a volatile mixture, and disseminated infections with NTM are extremely frequent in the advanced stages of AIDS (Chap. 309). In this setting, it is fortunate that new molecular techniques based on DNA amplification accelerate diagnosis, identify common sources of infection, and reveal new types of NTM, while new antibiotics, such as the macrolides, the rifamycins, and the fluoroquinolones, offer improved options for treatment and prevention. In addition, highly active antiretroviral therapy (HAART) has had a dramatic impact. By preventing and reversing immunodeficiency, HAART (Chap. 309) also prevents and reverses NTM infections.

## NTM INFECTIONS IN AIDS AND OTHER IMMUNODEFICIENCIES

### DISSEMINATED INFECTIONS

**Etiology** The majority of mycobacterial infections in immunocompromised hosts are caused by organisms belonging to the group referred to as the *M. avium* complex (MAC). This group has always been considered to include *M. avium* and *M. intracellulare* (designated by the abbreviation *MAI*) and in the past encompassed *M. scrofulaceum* as well (hence the abbreviation *MAIS*). With the development and marketing of diagnostic probes that distinguish *M. avium* from *M. intracellulare*, it has become clear that the vast majority of disseminated "MAC" infections in AIDS are actually caused by *M. avium*. Thus, from a microbiologic standpoint, this designation is now obsolete. However, it is still used in clinical practice and will be employed in that context herein.

*M. genavense* causes systemic infections similar to those caused byMACorganisms. *M. genavense* does not grow well in culture and may therefore be missed in some instances. However, in a series of nearly 200 disseminatedNTMinfections from Switzerland, 13% of cases were due to *M. genavense*. Other NTM, including *M. xenopi*, *M. simiae*, *M. scrofulaceum*, *M. malmoense*, and *M. celatum*, may also be involved in such cases. In addition, AIDS patients with localized NTM diseases (see "Localized

Infections," below) often have positive blood cultures (e.g., patients with skin disease due to *M. haemophilum* or with lung disease due to *M. kansasii*).

**Epidemiology and Host Factors** Because gastrointestinal symptoms often predominate inNTMinfection and because the intestinal submucosa is intensely involved, ingestion seems logical as a primary route of infection. Many environments and animals teem with NTM (especiallyMACorganisms), including swamps in the southeastern United States, swine almost everywhere, piped water in New England and in Finland, and soil from potted plants in San Francisco. Birds are frequently infected with *M. genavense*. Skin-test data and humoral antibody patterns point to widespread exposure. However, a direct connection of the environment to the patient is often lacking, and it is not always clear whether strains found in the environment are pathogenic in humans. In an exhaustive study of dietary factors, patients with NTM were found to have consumed more hard cheese than controls without NTM, but no NTM could be found in samples of cheese. At present, the epidemiologic evidence is not strong enough to serve as a basis for dietary recommendations in persons at high risk of NTM infection. There is no evidence for nosocomial spread of NTM from patient to patient; however, hospital hot-water systems have been suspected as the source of isolated clusters of cases. Whereas regional variations in the environmental frequency of NTM are striking, it is difficult to correlate these variations with the frequency of NTM infection among HIV-infected patients.

Disseminated infections with NTMoccur almost exclusively in severely immunosuppressed patients, usually those with AIDS. Rarely, such infections are found in patients immunosuppressed for other reasons, including transplant recipients, and patients with leukemia (in particular, hairy cell leukemia) or lymphoma. Cases in children may suggest the presence of a congenital immunodeficiency disease, such as a deficiency in the receptors for interferon g(IFN-g) or interleukin (IL) 12. Finally, rare cases of dissemination occur in immunocompetent patients who have extensive pulmonary disease (see "NTM Infections in Immunocompetent Patients," below).

In patients with AIDS, the risk ofNTMinfection correlates well with the degree of depletion of CD4+ lymphocytes. Disseminated NTM disease is rare among patients with >100 CD4+ cells per microliter; however, among patients with <10 CD4+ lymphocytes per microliter, the actuarial probability of having a blood culture positive for NTM reaches 40% after 1 year.HAARThas greatly diminished the overall incidence of NTM disease in AIDS. Current treatment recommendations suggest starting HAART when the CD4+ count falls below 500/uL. At these levels, NTM disease does not occur. In extremely immunosuppressed patients who start HAART, the CD4+ count typically rises above 100/uL within a few months; such patients are again unlikely to develop NTM disease.

**Clinical Manifestations** As has already been mentioned, disseminated infection withNTM is essentially a disease of advanced immunodeficiency. In HIV-infected patients, the median CD4+ lymphocyte count at the time of diagnosis is ~10/uL. Certainly, other diagnoses should be considered first when a patient with symptoms suggestive of NTM infection has>100 CD4+ cells per microliter. Prospective monthly blood cultures have shown that NTM bacteremia often causes few or no symptoms. In clinical practice, however, cultures are not performed if the patient is asymptomatic.

DisseminatedNTMinfection should be suspected on the basis of prolonged fever (sometimes of varying intensity -- particularly at first -- and accompanied by night sweats) and weight loss. Signs of abdominal involvement that may be evident on computed tomography or ultrasonography include enlargement of the liver and spleen and swelling of abdominal lymph nodes, which may result in diarrhea and/or abdominal pain. Anemia and leukopenia are frequently documented; although it is tempting to relate these abnormalities to infection of bone marrow by NTM, multiple factors are usually involved.

In short, the clinical picture of infection withNTM is not distinctive. Many other conditions, including abdominal lymphoma, the HIV wasting syndrome, *Salmonella* or *Campylobacter* infection, cryptosporidiosis, or microsporidiosis, may mimic (and coexist with) disseminated NTM infection. As stated earlier, suspicion of such infection should prompt a request for blood cultures.

**Diagnosis** Blood cultures on special media are the cornerstone of the diagnosis ofNTMinfection, both in patients with organ involvement and in those without. In most symptomatic patients, the intensity of mycobacteremia is such that most or all blood cultures are positive. Therefore, the performance of multiple, repetitive cultures at short intervals is not worthwhile. Rather, in clinical practice, two or three blood cultures are sufficient. In one study, the results of prospective cultures varied, and these variations (positive followed by negative or vice versa) were unrelated to symptom status. As mentioned above, liquid cultures (e.g., the Bactec system) are likely to become positive earlier (within 7 to 14 days) and are therefore preferred to cultures on solid medium. In patients infected with *M. genavense* or *M. xenopi* and in patients being treated forMACinfection, the interval to culture positivity may be much longer. In rare cases, organ involvement in NTM infection may be found to be widespread at autopsy despite multiple negative blood cultures during life.

Because the liver and bone marrow are often involved in disseminatedNTMinfection, the bacteria may be visible in acid-fast-stained biopsy samples from these sites. Presumptive diagnosis by examination of a biopsied liver specimen saves time. The yield has been as high as 50% in patients with clearly abnormal values in liver function tests. However, the yield of this method has been disappointing in patients with suspected NTM infection, negative blood cultures, and normal or nearly normal results in liver function tests.

## TREATMENT

Compared with *M. tuberculosis*,NTM are of low virulence. NTM tend to affect severely immunosuppressed patients, who usually have many other medical problems. Treatment is complex, relies on the use of multiple drugs with numerous adverse effects, and may interfere with antiretroviral therapy.

The drugs used for the treatment of disseminatedNTMinfection are different from those used against tuberculosis (Table 171-1;Chaps. 168 and169). In particular, isoniazid has little effect onMACorganisms. The best method for antibiotic sensitivity testing of NTM is controversial, and the question of what relation -- if any -- exists between in vitro

resistance and treatment failure remains unanswered. From the clinician's viewpoint, growth inhibition in liquid cultures is preferred to other methods of sensitivity testing because the results become available within 7 days.

The agents most active againstMACorganisms are the macrolides clarithromycin and azithromycin. Both of these drugs are well absorbed from the gastrointestinal tract and well concentrated in macrophages and tissues, where their levels exceed those in plasma by more than 10-fold. Given alone, either drug can render blood cultures negative in a substantial proportion of cases. However, resistance (due to a single point mutation in the gene coding for the large ribosomal subunit) invariably develops, andNTMreappear in the bloodstream.

A majority ofMACstrains are sensitive to ethambutol, ciprofloxacin, clofazimine, amikacin, rifampin, and rifabutin; that is, the concentrations of these drugs attainable in serum are inhibitory in vitro. However, none of these drugs consistently reduces the intensity of mycobacteremia when used alone. The preferred regimen for treatment of disseminatedNTMinfections is the combination of rifabutin (300 to 600 mg/d), clarithromycin (1 g twice daily), and ethambutol (900 mg/d). In a randomized trial, this regimen was superior to the combination of rifampin, clofazimine, ciprofloxacin, and ethambutol, with more rapid resolution of bacteremia and increased survival. The higher dose of rifabutin was more effective but frequently caused uveitis. This side effect is of special concern when rifabutin is used in combination with ritonavir, which increases the concentration of a toxic metabolite. Among the HIV protease inhibitors, indinavir and nelfinavir may be used in combination with rifabutin.

The inclusion of intravenous amikacin in multidrug regimens has not conferred additional benefit. Nonetheless, this drug may be useful in certain cases -- e.g., when resistance to clarithromycin develops or when severe gastrointestinal symptoms interfere with oral therapy. In addition, amikacin may prevent the emergence of resistance to clarithromycin when the two drugs are used concurrently.

It is not clear how long therapy needs to be administered. Older regimens did not eradicateMAC, and many experts recommended lifelong treatment. Unfortunately, multidrug regimens are often poorly tolerated. In patients whose symptoms have lessened, whose blood cultures have become negative, and whose CD4+counts have recovered to >100/uL withHAART, it is reasonable to discontinue antimycobacterial treatment.

In vitro and in experimental animals, cytokines such asIL-12, granulocyte-macrophage colony-stimulating factor, andIFN-gact synergistically with antibiotics againstMAC. In a small-scale pilot trial including seven HIV-negative patients, IFN-g was beneficial.

Encapsulation of many drugs into liposomes enhances their effect in animal models because both liposomes andMAC are ingested by macrophages. Relevant data from studies of humans are still scarce, however.

Disseminated infections caused byNTMother than MAC have been too rare for therapy to be evaluated in controlled trials. The presently recommended treatment for these infections is the same as that for disseminated MAC infections. In particular, *M.*

*genavense* seems to be sensitive to clarithromycin and rifabutin.

**Prevention** As has been discussed, disseminated infection withMACoccurs almost exclusively in persons severely immunocompromised by HIV infection. Therefore, the best approach to the prevention of MAC infections is the prevention and reversal of immunodeficiency byHAART. In patients whose HIV is resistant to HAART and who are severely immunosuppressed, with CD4+ counts<100/uL, prophylaxis with rifabutin (300 mg/d), clarithromycin (500 mg once or twice daily), or azithromycin (1200 mg weekly) is likely to decrease the incidence of positive blood cultures by ~60%. Patients receiving prophylaxis have also had less fever, experienced less fatigue, and survived longer than patients not receiving prophylaxis. Although breakthrough bacteremia involving resistant organisms is a concern, this condition has not developed with rifabutin prophylaxis and is rare with clarithromycin. However, it is standard practice to rule out preexisting disseminatedNTMinfection (by blood culture) before starting prophylaxis.

### LOCALIZED INFECTIONS

**Pulmonary Disease** The significance of isolation ofNTM from the airways of AIDS patients merits special discussion. In general, HIV-infected patients who have NTM in sputum or bronchoalveolar lavage fluid but have little evidence of lung damage require no treatment. *M. avium* only rarely causes significant pulmonary disease in AIDS; its isolation from sputum in the absence of radiographic changes is usually without clinical significance. In contrast, the isolation of *M. kansasii* from the lung is clinically significant: this organism causes a disease -- often predominant in the upper lobes -- that resembles pulmonary tuberculosis, with fever, cough, infiltrates, and cavities. Blood cultures are often positive. Drugs active against *M. tuberculosis*, such as rifampin (600 mg/d) and isoniazid (300 mg/d), are also effective against *M. kansasii*; treatment is generally continued for 18 to 24 months, although some data suggest that 12 months may be adequate.

**Skin Disease** MACorganisms, which frequently cause disseminated disease with positive blood cultures in AIDS, are also rarely associated with heterogeneous skin manifestations, such as nodules, ulcers, areas of erythema, pustules, abscesses, or panniculitis. Skin biopsies and blood cultures establish the diagnosis.

***M. haemophilum*** In contrast toMACorganisms, *M. haemophilum* has a tendency to involve the skin, bones, joints, and lungs, although most patients also have positive blood cultures. Skin lesions are nodular, may ulcerate, and are disseminated. In the absence of specific data, treatment should follow the guidelines for MAC infection.

## NTM INFECTIONS IN IMMUNOCOMPETENT PATIENTS

### PULMONARY DISEASE

**Etiology** TheNTM most frequently causing pulmonary infections are *M. intracellulare*, *M. avium*, and *M. kansasii*. Many other species, such as *M. xenopi*, *M. malmoense*, and *M. interjectum*, can also be involved in these infections. Identification of the specific pathogen is important in the choice among the various therapeutic strategies. For example, *M. kansasii* responds to antituberculosis drugs, including isoniazid.

**Epidemiology and Host Factors** As has already been noted,NTM are ubiquitous in the environment, but their pathogenicity is low. Preexisting lung disease (e.g., chronic obstructive airway disease, cancer, previous tuberculosis, bronchiectasis, cystic fibrosis, and silicosis, with cavities and bronchiectases) is the main predisposing factor for pulmonary disease due to NTM.

Anecdotal evidence suggests that the proportion of patients without underlying lung pathology who are developing pulmonary disease due toNTM is increasing. These patients are usually elderly; many are women with pectus excavatum or scoliosis. In the latter elderly women, the lingula and the right middle lobes are particularly involved. Somewhat whimsically, the disease in these patients has been called "Lady Windermere syndrome" after the main character in Oscar Wilde's play *Lady Windermere's Fan*, who went to extremes to refrain from coughing.

**Clinical Manifestations** Most immunocompetent patients with pulmonaryNTMinfection present with chronic cough, low-grade fever, and malaise; some present with hemoptysis. These symptoms may be masked by those of the underlying disease process.

**Diagnosis** In contrast to the isolation of *M. tuberculosis*, of which even a single colony -- whatever its origin -- is clinically significant, the isolation of NTMfrom the sputum never in itself proves the existence of disease. NTM are frequently commensals and colonize both diseased and normal airways. Because treatment of NTM infection is complicated, it is important that the diagnosis be certain. The American Thoracic Society has formulated the following minimal guidelines for the diagnosis of pulmonary NTM disease: "evidence, such as an infiltrate visible on a chest roentgenogram, of disease, the cause of which has not been determined by careful clinical and laboratory studies, and...isolation of multiple colonies of the same strain of mycobacteria repeatedly, usually in the absence of other pathogens." For patients who have pulmonary infiltrates but not cavities, these criteria may not be specific enough; some patients are found to have cleared NTM after a 1-month trial of bronchial hygiene alone (inhalation of saline and bronchodilators to induce cough and sputum production). The detection by computed tomography of bronchiectases and nodular infiltrates in the same lobe may be particularly suggestive of NTM infection.

**TREATMENT**

Lung disease due toNTM may be managed by follow-up without treatment, by resection, or by drug therapy. No randomized trial has determined which is the best option. In retrospectively analyzed case series, patients undergoing surgery have had a better outcome than those treated only with drugs. However, selection bias has probably influenced these results since patients with extensive lung disease are poor candidates for surgery.

As in HIV-infected patients, immunocompetent patients with minimal disease do not need treatment at all. Likewise,NTMdisease may present as a solitary pulmonary nodule that, once resected (to confirm or exclude a diagnosis of cancer), requires no further drug treatment.

Most other patients with pulmonaryNTMdisease are treated with antimicrobials; in addition, they may or may not undergo surgery. The drugs available for the treatment of infection with *M. avium* or *M. intracellulare* have already been discussed. The regimens recommended for disseminatedMACinfection are preferred, although large doses of clarithromycin are often poorly tolerated by elderly patients. *M. intracellulare* may be easier to treat and eradicate than *M. avium*. In two small open studies, single-agent treatment with clarithromycin (500 mg twice daily) led to improvements detected by chest radiography and sputum culture.

Indications for surgery are difficult to establish but include a disappointing response to antibiotics, the presence of localized disease, and the absence of contraindications (especially impaired respiratory functions). Ideally, drug treatment should begin before surgery and should render the sputum negative by the time of the operation.

In contrast toMACorganisms, *M. kansasii* is predictably sensitive to antituberculosis agents. Treatment should consist of isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 to 25 mg/kg per day). The optimal duration of therapy is unknown, but most patients have been treated for 18 to 24 months; 12 months may suffice. Sulfamethoxazole is recommended for the occasional patient whose infection relapses after *M. kansasii* becomes resistant to rifampin.

## LYMPHADENITIS

NTMare among the causes of localized lymphadenitis. This disease occurs mostly in children between the ages of 1 and 5 years. Painless swelling of one node or a group of nodes usually affects the anterior cervical chain. Nodes may rapidly increase in size, with the formation of fistulas to the skin. *M. scrofulaceum* orMACorganisms most commonly cause NTM lymphadenitis, although many other species may be involved. Once tuberculosis has been excluded, the treatment of choice is excision without chemotherapy. When excision is dangerous because of proximity to the facial nerve, aspiration combined with chemotherapy may be effective.

## SKIN DISEASE DUE TO NTM

**Swimming-Pool and Fish-Tank Granuloma (Fig. 171-CD1)** Between 1 week and 2 months (usually 2 to 3 weeks) after contact with contaminated tropical fish tanks, swimming pools, or saltwater fish, a small violet nodule or pustule may appear at a site of minor trauma. This lesion may evolve to form a crusted ulcer or small abscess or may remain warty. Lesions are multiple and disseminated on occasion -- particularly, but not exclusively, in immunosuppressed patients. The causative organism is *M. marinum*. The patient's clinical history, combined with the isolation of *M. marinum* after biopsy and culture, establishes the diagnosis. Lesions often heal spontaneously. In cases of persistence or dissemination, rifampin (300 to 600 mg/d) in combination with ethambutol (15 to 25 mg/kg per day), trimethoprim-sulfamethoxazole (160/800 mg twice daily), or minocycline (100 mg/d) may be tried for a period of at least 3 months. Very rarely, a similar clinical picture is produced by *M. gordonae*, a frequently isolated but usually nonpathogenic species.

**Buruli Ulcer** In many tropical areas throughout the world, *M. ulcerans* may cause an itching nodule on the arms or legs, which then breaks down to form a shallow ulcer of variable size (Fig. 171-CD2). The course of this condition is usually prolonged. *M. ulcerans* is difficult to culture; plates need to be incubated at low temperature. Excision constitutes the usual therapy. Treatment with rifampin, clofazimine, or trimethoprim-sulfamethoxazole has met with variable success.

## NTMINFECTIONS OF SOFT TISSUE, TENDONS, BONES, AND JOINTS

**Infections Linked to Injections and Surgery** Occasionally, mycobacteria are isolated from nodular skin lesions of hospitalized patients, particularly those who are immunosuppressed (Fig. 171-CD3); in some instances there is associated lymphatic spread. Many cases are linked to injection; diabetic patients are at especially high risk. In ophthalmology, mycobacteria may cause keratitis and corneal ulceration after surgery or injury. Epidemics of mycobacterial infection following cardiac surgery have been linked to contaminated ice packs and contaminated porcine heart valves. These infections are usually due to *M. fortuitum*, *M. chelonae*, or *M. abscessus*, which are referred to collectively as the *M. fortuitum* complex. These are the so-called rapidly growing mycobacteria: colonies on solid medium appear 3 to 7 days after inoculation. As organisms may fail to grow at 37°C, incubation at 30 to 33°C is recommended. These mycobacteria are notoriously resistant to most antituberculosis drugs. Debridement is best combined with administration of two or three of the antibiotics mentioned inTable 171-1.

**Infections of Tendons, Joints, and Bones** In rare cases, mycobacteria invade deep tissues after direct inoculation, via contiguous spread from superficial sites of infection, or through the bloodstream.MACorganisms and *M. ulcerans* are most often cited in these instances. *M. szulgai* seems to be involved particularly frequently in olecranon bursitis.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 9 -SPIROCHETAL DISEASES

# 172. SYPHILIS - *Sheila A. Lukehart*

## DEFINITION

Syphilis, a chronic systemic infection caused by *Treponema pallidum* subspecies *pallidum*, is usually sexually transmitted and is characterized by episodes of active disease interrupted by periods of latency. After an incubation period averaging 2 to 6 weeks, a primary lesion appears, often associated with regional lymphadenopathy. A secondary bacteremic stage, associated with generalized mucocutaneous lesions and generalized lymphadenopathy, is followed by a latent period of subclinical infection lasting many years. In about one-third of untreated cases, the tertiary stage is characterized by progressive destructive mucocutaneous, musculoskeletal, or parenchymal lesions; aortitis; or symptomatic central nervous system (CNS) disease.

## ETIOLOGY

The Spirochaetales include three genera that are pathogenic for humans and for a variety of other animals: *Leptospira*, which causes human leptospirosis; *Borrelia*, which causes relapsing fever and Lyme disease; and *Treponema*, which causes the diseases known as treponematoses. The genus *Treponema* includes *T. pallidum* subspecies *pallidum*, which causes venereal syphilis; *T. pallidum* subspecies *pertenue*, which causes yaws; *T. pallidum* subspecies *endemicum*, which causes endemic syphilis or bejel; and *T. carateum*, which causes pinta (Chap. 173). Other *Treponema* species found in the human mouth, genital mucosa, and gastrointestinal tract have no proven pathogenic role in human disease. These spirochetes can be confused with *T. pallidum* on dark-field examination. An oral treponeme that is very closely related to *T. pallidum* antigenically has been found to be significantly associated with periodontitis and acute necrotizing ulcerative gingivitis; its etiologic role in these gum diseases is unknown. None of the four pathogenic treponemes has yet been cultured in quantity. Until recently, the subspecies were distinguished primarily by the clinical syndromes they produce. Recent studies have identified molecular signatures that can differentiate *T. pallidum* subspecies *pallidum* from the other pathogenic *T. pallidum* subspecies by culture-independent, polymerase chain reaction (PCR)-based methods.

*T. pallidum* subspecies *pallidum* (hereafter referred to simply as *T. pallidum*), a thin delicate organism with 6 to 14 spirals and tapered ends, measures 6 to 15 um in total length and 0.2 um in width. The cytoplasm is surrounded by a trilaminar cytoplasmic membrane, which in turn is surrounded by a delicate peptidoglycan layer providing some structural rigidity. This layer is surrounded by a lipid-rich outer membrane that contains relatively few integral membrane proteins. Six endoflagella wind around the cell body in a space between the inner cell wall and the outer membrane and may be the elements responsible for motility.

The sequencing of the genome of *T. pallidum* has yielded information about the organism's metabolic capabilities. *T. pallidum* lacks the genes required to synthesize enzyme cofactors, fatty acids, and nucleotides de novo. In addition, it lacks genes encoding the enzymes of the Krebs cycle and oxidative phosphorylation. To

compensate, the organism contains numerous genes predicted to code for transporters of amino acids, carbohydrates, and cations. In addition, the genome analyses and other studies have revealed the existence of a 12-member gene family (called *tpr*) that bears similarities to variable outer-membrane antigens of other spirochetes. Although the role of these encoded molecules has not yet been defined, the TprK antigen appears to be preferentially expressed and serves as a target of opsonic antibody.

The only known natural host for *T. pallidum* is the human. *T. pallidum* can infect many mammals, but only humans, higher apes, and a few laboratory animals regularly develop syphilitic lesions. Virulent strains of *T. pallidum* are grown and maintained in rabbits.

**EPIDEMIOLOGY**

Nearly all cases of syphilis are acquired by sexual contact with infectious lesions (i.e., the chancre, mucous patch, skin rash, or condyloma latum). Less common modes of transmission include nonsexual personal contact and infection in utero or following blood transfusions.

The total number of cases of syphilis reported annually in the United States fell steadily from 575,593 in 1943 to a low of 64,621 in 1987 -- an 88% decrease -- but then increased to 134,255 in 1990. The number of new cases of infectious syphilis reached a peak in 1947 and then fell to approximately 6000 in 1956; since then, a rather steady increase in infectious syphilis has been punctuated by four cycles of 7 to 10 years, each with a rapid rise and fall in incidence (with peaks in 1965, 1975, 1982, and 1990). Since 1990, the number of reported cases of infectious syphilis has again declined by >80%. In 1997, there were 8550 reported cases of primary and secondary syphilis and 46,540 cases of all stages.

The populations at highest risk for acquiring syphilis have changed. Between 1977 and 1982, approximately half of all patients with early syphilis in the United States were homosexual or bisexual men. Largely because of changing sexual practices in this population due to the AIDS epidemic, this proportion has decreased. The most recent epidemic of syphilis predominantly involved African-American heterosexual men and women and occurred largely in urban areas, where infectious syphilis has been correlated significantly with the exchange of sex for "crack" cocaine. The incidence of syphilis peaks at 15 to 34 years of age. The reported incidence is much higher among African Americans than in other ethnic groups and is higher in urban than in rural areas; 80% of infectious syphilis cases are reported from 15% of the counties in the United States.

The incidence of congenital syphilis roughly parallels that of infectious syphilis in females. The number of reported cases of congenital syphilis in infants£1 year of age was lowest (107 cases) in 1978, when infectious syphilis was most prevalent among homosexual and bisexual men. The dramatic increase in the incidence of primary and secondary syphilis among women from 1986 to 1990 resulted in a proportionate increase in the number of infants born with congenital syphilis -- to 3275 infants in 1991. The incidence of early syphilis among men and women has declined since 1991, as has the number of reported cases of congenital syphilis in infants (with 1049 cases in 1997).

It is important to note, however, that the case definition for congenital syphilis was broadened in 1989 and now includes all live or stillborn infants delivered to women with untreated or inadequately treated syphilis at delivery.

Approximately one of every two individuals named as sexual contacts of persons with infectious syphilis becomes infected. Many sexual contacts will already have developed manifestations of syphilis when they are first seen, and about 30% of apparently uninfected contacts who are examined within 30 days of exposure actually have incubating infection and will later develop infectious syphilis if not treated. Thus, the identification and "epidemiologic" treatment of all recently exposed sexual contacts constitute an important aspect of syphilis control. Also important is the identification of infected persons by serologic testing of pregnant women, persons admitted to hospitals, military inductees, and persons undergoing examination in physicians' offices. Still controversial are laws and regulations requiring routine premarital serologic testing for syphilis, where -- though national data are not available -- the yield is undoubtedly lower.

## NATURAL COURSE AND PATHOGENESIS OF UNTREATED SYPHILIS

*T. pallidum* rapidly penetrates intact mucous membranes or microscopic abrasions in skin and within a few hours enters the lymphatics and blood to produce systemic infection and metastatic foci long before the appearance of a primary lesion. Blood from a patient with incubating or early syphilis is infectious. The generation time of *T. pallidum* during early active disease in vivo is estimated to be 30 to 33 h, and the incubation period of syphilis is inversely proportional to the number of organisms inoculated. The concentration of treponemes generally reaches at least $10^7$ per gram of tissue before the appearance of a clinical lesion. On the basis of intradermal injection of graded doses of *T. pallidum* into eight volunteers, the 50% infectious dose was calculated to be 57 organisms. The median incubation period in humans (about 21 days) suggests an average inoculum of 500 to 1000 infectious organisms for naturally acquired disease. The incubation period (from inoculation until the primary lesion becomes discernible) rarely exceeds 6 weeks. Subcurative therapy during the incubation period may delay the onset of the primary lesion, but it is not certain that such treatment reduces the probability that symptomatic disease will ultimately develop.

The primary lesion appears at the site of inoculation, usually persists for 4 to 6 weeks, and then heals spontaneously. Histopathologic examination of primary lesions shows perivascular infiltration, chiefly by lymphocytes (including CD8+ and CD4+ cells), plasma cells, and macrophages, with capillary endothelial proliferation and subsequent obliteration of small blood vessels. The CD4+ infiltration displays a $T_H1$-type cytokine profile consistent with the activation of macrophages. At this time *T. pallidum* is demonstrable in the chancre in spaces between epithelial cells; within invaginations or phagosomes of epithelial cells, fibroblasts, plasma cells, and the endothelial cells of small capillaries; within lymphatic channels; and in the regional lymph nodes. Phagocytosis of organisms by activated macrophages ultimately causes their destruction, which results in spontaneous resolution of the chancre.

The generalized parenchymal, constitutional, and mucocutaneous manifestations of secondary syphilis usually appear about 6 to 8 weeks after healing of the chancre,

although 15% of patients with secondary syphilis still have persisting or healing chancres. In other patients, secondary lesions may appear several months after the chancre has healed, and some patients may enter the latent stage without ever recognizing secondary lesions. The histopathologic features of secondary maculopapular skin lesions are hyperkeratosis of the epidermis; capillary proliferation with endothelial swelling in the superficial corium; and dermal papillae with transmigration of polymorphonuclear leukocytes and, in the deeper corium, perivascular infiltration by monocytes, plasma cells, and lymphocytes. Treponemes are found in many tissues, including the aqueous humor of the eye and the cerebrospinal fluid (CSF). Invasion of theCNS by *T. pallidum* occurs during the first weeks or months of infection, and CSF abnormalities are detected in as many as 40% of patients during the secondary stage. Clinical hepatitis and immune complex-induced membranous glomerulonephritis are relatively rare but recognized manifestations of secondary syphilis; liver function tests may yield abnormal results in up to a quarter of patients with early syphilis. Generalized nontender lymphadenopathy is noted in 85% of patients with secondary syphilis. The paradoxical appearance of secondary manifestations despite high titers of antibody (including immobilizing antibody) to *T. pallidum* is unexplained but may result from changes in expression of surface antigens. Secondary lesions subside within 2 to 6 weeks, and the infection enters the latent stage, which is detectable only by serologic testing. In the preantibiotic era, up to 25% of untreated patients experienced at least one generalized or localized mucocutaneous relapse, usually during the first year; therefore, identification and examination of sexual contacts are most important for patients with syphilis of<1 year's duration. Recurrent generalized rash is now rare.

In the preantibiotic era, about one-third of patients with untreated latent syphilis developed clinically apparent tertiary disease (Fig. 128-CD5); today, in industrialized countries, specific treatment and coincidental therapy for early and latent syphilis have all but eliminated tertiary disease except for sporadic cases of neurosyphilis in persons infected with HIV. In the past, the most common type of tertiary disease was the gumma, a usually benign granulomatous lesion. Today, gummas are very uncommon. Cardiovascular syphilis, now also rare, is caused by obliterative small-vessel endarteritis, usually involving the vasa vasorum of the ascending aorta and resulting in aneurysm. AsymptomaticCNSinvolvement is demonstrable in up to 25% of patients with late latent syphilis. The factors that contribute to the development and progression of tertiary disease are unknown.

The course of untreated syphilis was studied retrospectively in a group of nearly 2000 patients with primary or secondary disease diagnosed clinically (the Oslo Study, 1891-1951) and prospectively in 431 African-American men with seropositive latent syphilis of 3 or more years' duration (the notorious Tuskegee Study, 1932-1972). In the Oslo Study, 24% of patients developed relapsing secondary lesions within 4 years, and 28% eventually developed one or more manifestations of tertiary syphilis. Cardiovascular syphilis, including aortitis, was detected in 10% of patients, none of whom had been infected before age 15; 7% of patients developed symptomatic neurosyphilis, and 16% developed benign tertiary syphilis (gummas of the skin, mucous membranes, and skeleton). Syphilis was the primary cause of death in 15% of men and 8% of women. Cardiovascular syphilis was documented in 35% of men and 22% of women who eventually came to autopsy. In general, serious late complications were nearly twice as common among men as among women.

The Tuskegee Study showed that the death rate among untreated African-American men with syphilis (25 to 50 years old) was 17% higher than that among uninfected subjects and that 30% of all deaths were attributable to cardiovascular orCNSsyphilis. By far the most important factor in increased mortality was cardiovascular syphilis. Anatomic evidence of aortitis was found in 40 to 60% of autopsied subjects with syphilis (versus 15% of control subjects), while CNS syphilis was found in only 4%. Rates of hypertension were also higher among the infected subjects. The ethical issues eventually raised by this study, begun in the preantibiotic era but continuing into the early 1970s, had a major influence on the development of current guidelines for human medical experimentation, and the history of the study may still contribute to a reluctance of some African Americans to participate as subjects in clinical research.

These two studies both showed that about one-third of patients with untreated syphilis develop clinical or pathologic evidence of tertiary syphilis, that about one-fourth die as a direct result of tertiary syphilis, and that there is additional excess mortality not directly attributable to tertiary syphilis.

## MANIFESTATIONS

**Primary Syphilis** The typical primary chancre usually begins as a single painless papule that rapidly becomes eroded and usually becomes indurated, with a characteristic cartilaginous consistency on palpation of the edge and base of the ulcer (see Plate IID-47,Fig. 172-CD1). In heterosexual men the chancre is usually located on the penis, whereas in homosexual men it is often found in the anal canal or rectum, in the mouth, or on the external genitalia. In women, common primary sites are the cervix and labia. Consequently, primary syphilis goes unrecognized in women and homosexual men more often than in heterosexual men.

Atypical primary lesions are common. The clinical appearance depends on the number of treponemes inoculated and on the immunologic status of the patient. A large inoculum produces a dark-field-positive ulcerative lesion in nonimmune volunteers but may produce a small dark-field-negative papule, an asymptomatic but seropositive latent infection, or no response at all in individuals with a history of syphilis. A small inoculum may produce only a papular lesion, even in nonimmune individuals. Therefore, syphilis should be considered even in the evaluation of trivial or atypical dark-field-negative genital lesions. The genital lesions that most commonly must be differentiated from those of primary syphilis include traumatic superinfected lesions, lesions of herpes simplex virus infection (Chap. 182), and lesions of chancroid (Chap. 149). *Primary genital herpes* may produce inguinal adenopathy, but the nodes are tender and the lesions consist of multiple painful vesicles, which later ulcerate and are often accompanied by systemic symptoms, including fever. *Recurrent genital herpes* typically begins with a unilateral cluster of painful vesicles, usually without associated adenopathy. *Chancroid* produces painful, superficial, exudative, nonindurated ulcers, more often multiple than in syphilis (seePlate IID-54); adenopathy is common, can be either unilateral or bilateral, is tender, and may be suppurative.

Regional lymphadenopathy usually accompanies the primary syphilitic lesion, appearing within 1 week of the onset of the lesion. The nodes are firm, nonsuppurative, and

painless. Inguinal lymphadenopathy is bilateral and may occur with anal as well as with external genital chancres. Rectal chancres result in perirectal lymphadenopathy, while chancres of the cervix and vagina result in iliac or perirectal adenopathy. The chancre generally heals within 4 to 6 weeks (range, 2 to 12 weeks), but lymphadenopathy may persist for months.

**Secondary Syphilis** The protean manifestations of the secondary stage usually include localized or diffuse symmetric mucocutaneous lesions and generalized nontender lymphadenopathy. The healing primary chancre is still present in 15% of cases. The skin rash consists of macular, papular, papulosquamous, and occasionally pustular syphilides; often more than one form is present simultaneously. The eruption may be very subtle. Approximately 25% of patients with a discernible rash of secondary syphilis may be unaware that they have dermatologic manifestations. Initial lesions are bilaterally symmetric, pale red or pink, nonpruritic, discrete, round macules that measure 5 to 10 mm in diameter and are distributed on the trunk and proximal extremities (see Plate IID-50). After several days or weeks, red papular lesions 3 to 10 mm in diameter also appear. These lesions, which may progress to necrotic lesions (resembling pustules) in association with increasing endarteritis and perivascular mononuclear infiltration, are distributed widely, frequently involve the palms and soles (see Plate IID-48), and may occur on the face and scalp. Tiny papular *follicular syphilides* involving hair follicles may result in patchy alopecia (alopecia areata), with loss of scalp hair, eyebrows, or beard in up to 5% of cases. Progressive endarteritis obliterans and ischemia result in superficial scaling of papules (*papulosquamous syphilides*) and eventually may lead to central necrosis (*pustular syphilides*).

In warm, moist, intertriginous body areas, including the perianal area, vulva, scrotum, inner thighs, axillae, and skin under pendulous breasts, papules can enlarge and become eroded to produce broad, moist, pink or gray-white, highly infectious lesions called *condylomata lata* (see Plate IID-49); these lesions develop in 10% of patients with secondary syphilis. Superficial mucosal erosions, called *mucous patches*, occur in 10 to 15% of patients and may involve the lips, oral mucosa, tongue (Fig. 172-1), palate, pharynx, vulva and vagina, glans penis, or inner prepuce. The typical mucous patch is a painless silver-gray erosion surrounded by a red periphery. During relapses of secondary syphilis, condylomata lata are particularly common, and skin lesions tend to be asymmetrically distributed and more infiltrated, resembling skin lesions of late syphilis. These characteristics may reflect increasing cellular immunity.

Constitutional symptoms that may accompany or precede secondary syphilis include sore throat (15 to 30%), fever (5 to 8%), weight loss (2 to 20%), malaise (25%), anorexia (2 to 10%), headache (10%), and meningismus (5%). *Acute meningitis* occurs in only 1 to 2% of cases, but numbers of cells and levels of protein in CSF are increased in ³30% of cases. *T. pallidum* has been recovered from CSF during primary and secondary syphilis in 30% of cases; this finding is often but not always associated with other CSF abnormalities.

Less common complications of secondary syphilis include hepatitis, nephropathy, gastrointestinal involvement (hypertrophic gastritis, patchy proctitis, ulcerative colitis, or a rectosigmoid mass), arthritis, and periostitis. Ocular findings that suggest secondary syphilis include otherwise-unexplained pupillary abnormalities, optic neuritis, and a

retinitis pigmentosa syndrome as well as the classic iritis (especially granulomatous iritis) or uveitis. The diagnosis of secondary syphilis is often considered only after the patient fails to respond to steroid therapy. Anterior uveitis has been reported in 5 to 10% of patients with secondary syphilis, and *T. pallidum* has been demonstrated in the aqueous humor from these patients. *Syphilitic hepatitis* is distinguished by an unusually high serum level of alkaline phosphatase and by a nonspecific histologic appearance that is unlike that of viral hepatitis and includes moderate inflammation with polymorphonuclear leukocytes and lymphocytes, some hepatocellular damage, and no cholestasis. *Renal involvement* produces proteinuria associated with an acute nephrotic syndrome (or rarely with hemorrhagic glomerulonephritis) and is characterized by subepithelial electron-dense deposits and glomerular immune complexes -- findings suggesting immune-complex glomerulonephritis.

**Latent Syphilis** Positive serologic tests for syphilis, together with a normalCSFexamination and the absence of clinical manifestations of syphilis, indicate a diagnosis of latent syphilis. The diagnosis is often suspected on the basis of a history of primary or secondary lesions, a history of exposure to syphilis, or the delivery of an infant with congenital syphilis. A previous negative serologic test or a history of lesions or exposure may help establish the duration of latent infection. *Early latent* syphilis encompasses the first year after infection, while *late latent* syphilis (beginning³1 year after infection in the untreated patient) is associated with relative immunity to infectious relapse and with increasing resistance to reinfection. *T. pallidum* may still seed the bloodstream intermittently during this stage. Pregnant women with latent syphilis may infect the fetus in utero. Moreover, syphilis has been transmitted through the transfusion of blood from patients with latent syphilis of many years' duration. It was previously thought that untreated late latent syphilis had three possible outcomes: (1) it could persist throughout the lifetime of the infected individual, (2) it could end in the development of late syphilis, or (3) it could end with the spontaneous cure of infection, with reversion of serologic tests to negative. It is now apparent, however, that the more sensitive treponemal antibody tests rarely, if ever, become negative without treatment. About 70% of untreated patients with latent syphilis never develop clinically evident late syphilis, but the occurrence of spontaneous cure is in doubt.

**Late Syphilis** The slowly progressive inflammatory disease leading to tertiary manifestations begins early during the pathogenesis of syphilis, although these manifestations may not become clinically apparent for years. Early syphilitic aortitis becomes evident soon after secondary lesions subside, and patients who developCSFabnormalities during the early stages of syphilis appear to be at highest risk of late neurologic complications.

*Asymptomatic Neurosyphilis* CNSsyphilis represents a continuum comprising early invasion, usually within the first weeks or months of infection, and asymptomatic involvement, which may or may not lead to neurologic manifestations. Traditionally, the diagnosis of asymptomatic neurosyphilis has been made in patients who lack neurologic symptoms and signs and who haveCSFabnormalities including mononuclear pleocytosis, increased protein concentrations, or a reactive Venereal Disease Research Laboratory (VDRL) slide test. Such abnormalities are found in up to one-quarter of patients with untreated late latent syphilis, and it is these patients who are known to be at risk for neurologic complications. However, in primary and secondary syphilis, *T.*

*pallidum* can be isolated from CSF of 40% of patients even in the absence of other CSF abnormalities. Although the therapeutic implications of these findings in early syphilis are uncertain, it seems appropriate to conclude that even patients with early syphilis who have such findings do indeed have asymptomatic neurosyphilis and should be treated for neurosyphilis. In patients with untreated asymptomatic neurosyphilis, the overall cumulative probability of progression to clinical neurosyphilis is about 20% in the first 10 years but increases with time; the likelihood is highest among patients with the greatest degree of pleocytosis or protein elevation. Patients with untreated latent syphilis and normal CSF probably run no risk of subsequent neurosyphilis.

*Symptomatic Neurosyphilis* Although mixed features are common, the major clinical categories of symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis. The last category includes general paresis and tabes dorsalis. The onset of symptoms usually comes <1 year after infection for meningeal syphilis, at 5 to 10 years for meningovascular syphilis, at 20 years for general paresis, and at 25 to 30 years for tabes dorsalis. However, symptomatic neurosyphilis, particularly in the antibiotic era, often presents not as a classic picture but rather as mixed and subtle or incomplete syndromes.

*Meningeal syphilis* may involve either the brain or the spinal cord, and patients may present with headache, nausea, vomiting, neck stiffness, cranial nerve palsies, seizures, and changes in mental status. *Meningovascular syphilis* reflects diffuse inflammation of the pia and arachnoid together with evidence of focal or widespread arterial involvement of small, medium, or large vessels. The most common presentation is a stroke syndrome involving the middle cerebral artery of a relatively young adult; however, unlike the usual thrombotic or embolic stroke syndrome of sudden onset, meningovascular syphilis often becomes manifest after a subacute encephalitic prodrome (with headaches, vertigo, insomnia, and psychological abnormalities), which is followed by a gradually progressive vascular syndrome.

The manifestations of *general paresis* reflect widespread parenchymal damage and include abnormalities corresponding to the mnemonic *paresis*: *p*ersonality, *a*ffect, *r*eflexes (hyperactive), *e*ye (e.g., Argyll Robertson pupils), *s*ensorium (illusions, delusions, hallucinations), *i*ntellect (a decrease in recent memory and in the capacity for orientation, calculations, judgment, and insight), and *s*peech. *Tabes dorsalis* presents as symptoms and signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia. Symptoms include ataxic wide-based gait and footslap; paresthesia; bladder disturbances; impotence; areflexia; and loss of position, deep pain, and temperature sensations. Trophic joint degeneration (Charcot's joints) and perforating ulceration of the feet can result from loss of pain sensation. The small, irregular Argyll Robertson pupil, a feature of both tabes dorsalis and paresis, reacts to accommodation but not to light. *Optic atrophy* also occurs frequently in association with tabes.

*Cardiovascular Syphilis* Cardiovascular manifestations are attributable to endarteritis obliterans of the vasa vasorum, which provide the blood supply to large vessels. This condition produces medial necrosis with destruction of elastic tissue, particularly in the ascending and transverse segments of the aortic arch, resulting in uncomplicated aortitis, aortic regurgitation, saccular aneurysm, or coronary ostial stenosis. Symptoms appear from 10 to 40 years after infection. Cardiovascular complications occur more

often and at an earlier age among men than among women and may be more common among African Americans than among whites. In the preantibiotic era, symptomatic cardiovascular complications developed in about 10% of persons with late untreated syphilis, and aortic regurgitation was two to four times as common as aneurysm. However, syphilitic aortitis was demonstrated at autopsy in about one-half of African-American men with untreated syphilis.

Linear calcification of the ascending aorta on chest x-ray films suggests asymptomatic syphilitic aortitis, as arteriosclerosis seldom produces this sign. Aortic dilation and a tambour quality to the sound of aortic closure are unreliable signs of aortitis. Syphilitic aneurysms -- usually saccular, occasionally fusiform -- do not lead to dissection. Approximately 1 in 10 aortic aneurysms of syphilitic origin involves the abdominal aorta, but these aneurysms tend to occur above the renal arteries, whereas arteriosclerotic abdominal aneurysms are usually found below the renal arteries. With increasing age, the nervous system is also affected in up to 40% of patients with cardiovascular syphilis.

*Late Lesions of the Eyes* Iritis associated with pain, photophobia, and dimness of vision or chorioretinitis occurs not only during secondary syphilis but also as a relatively common manifestation of late syphilis. Adhesions of the iris to the anterior lens may produce a fixed pupil, not to be confused with Argyll Robertson pupil.

*Late Benign Syphilis (Gumma)* Gummas may be multiple or diffuse but are usually solitary lesions that range from microscopic size to several centimeters in diameter. From a histologic perspective, gummas consist of a granulomatous inflammation with a central area of necrosis surrounded by mononuclear, epithelioid, and fibroblastic cells; occasional giant cells; and perivasculitis. Although rarely demonstrated microscopically, *T. pallidum* has reportedly been recovered from these lesions. The most commonly involved sites include the skin and skeletal system, the mouth and upper respiratory tract, the larynx, the liver, and the stomach; however, any organ may be involved. Gummas of the skin produce painless and indurated nodular, papulosquamous, or ulcerative lesions that form characteristic circles or arcs, with peripheral hyperpigmentation. Gummas are usually indolent and may heal spontaneously with scarring, but they may also be explosive in onset and are often destructive. These lesions may resemble those of many other chronic granulomatous conditions, including tuberculosis and sarcoidosis, leprosy, and deep fungal infections. Skeletal gummas most frequently involve the long bones of the legs, although any bone may be affected. Trauma may predispose a specific site to involvement. Presenting symptoms usually include focal pain and tenderness. Radiographic abnormalities with advanced gummas of bone include periostitis or destructive or sclerosing osteitis. Upper respiratory gummas can lead to perforation of the nasal septum or palate. Gummatous hepatitis may produce epigastric pain and tenderness as well as low-grade fever and may be associated with splenomegaly and anemia.

The histopathology and extensive tissue necrosis associated with gummas suggest delayed hypersensitivity to *T. pallidum*. Certain individuals appear to develop an exaggerated delayed-hypersensitivity response to *T. pallidum*, which presumably is mediated by sensitized T lymphocytes and macrophages. Because the histologic changes may be suggestive but are nonspecific, the diagnosis of late benign syphilis is confirmed by serologic testing and by therapeutic trial. Treatment with penicillin results

in rapid healing of active gummatous lesions.

**Congenital Syphilis** Transmission of *T. pallidum* from a syphilitic woman to her fetus across the placenta may occur at any stage of pregnancy, but the lesions of congenital syphilis generally develop after the fourth month of gestation, when fetal immunologic competence begins to develop. This timing suggests that the pathogenesis of congenital syphilis depends on the immune response of the host rather than on a direct toxic effect of *T. pallidum*. The risk of infection of the fetus during untreated early maternal syphilis is estimated to be 75 to 95%, decreasing to about 35% for maternal syphilis of>2 years' duration. Adequate treatment of the mother before the 16th week of pregnancy should prevent fetal damage. Untreated maternal infection may result in a rate of fetal loss of up to 40% (with stillbirth more common than abortion because of the late onset of fetal pathology), prematurity, neonatal death, or nonfatal congenital syphilis. Among infants born alive, only fulminant congenital syphilis is clinically apparent at birth, and these babies have a very poor prognosis. The most common clinical problem is the healthy-appearing baby born to a mother with a positive serologic test. Routine serologic testing in early pregnancy is considered cost-effective in virtually all populations, even in areas with a low prenatal prevalence of syphilis. Where the prevalence of syphilis is high and when the patient is at high risk, syphilis serology should be repeated in the third trimester and at delivery.

The manifestations of congenital syphilis can be divided into three types according to their timing: (1) early manifestations, which appear within the first 2 years of life (often between 2 and 10 weeks of age), are infectious and resemble the manifestations of severe secondary syphilis in the adult; (2) late manifestations, which appear after 2 years and are noninfectious; and (3) residual stigmata. The earliest sign of congenital syphilis is usually rhinitis, or "snuffles" (23%), which is soon followed by other mucocutaneous lesions (35 to 41%). These may include bullae (syphilitic pemphigus), vesicles, superficial desquamation, petechiae, and (later) papulosquamous lesions, mucous patches, and condylomata lata. The most common early manifestations are bone changes (61%), including osteochondritis, osteitis, and periostitis. Hepatosplenomegaly (50%), lymphadenopathy (32%), anemia (34%), jaundice (30%), thrombocytopenia, and leukocytosis are common.

Neonatal congenital syphilis must be differentiated from other generalized congenital infections, including rubella, cytomegalovirus or herpes simplex virus infection, and toxoplasmosis, as well as from erythroblastosis fetalis. Neonatal death is usually due to pulmonary hemorrhage, secondary bacterial infection, or severe hepatitis.

Late congenital syphilis is that which remains untreated after 2 years of age. In perhaps 60% of cases, the infection remains subclinical; the clinical spectrum in the remainder of cases differs in certain respects from that of acquired late syphilis in the adult. For example, cardiovascular syphilis rarely develops in late congenital syphilis, whereas interstitial keratitis is much more common and occurs between the ages of 5 and 25. Other manifestations associated with interstitial keratitis are eighth-nerve deafness and recurrent arthropathy. Bilateral knee effusions are known as *Clutton's joints*. Asymptomatic neurosyphilis is present in about one-third of untreated patients, and clinical neurosyphilis occurs in one-quarter of untreated individuals over 6 years of age. Gummatous periostitis occurs between the ages of 5 and 20 and, as in nonvenereal

endemic syphilis, tends to cause destructive lesions of the palate and nasal septum.

Characteristic stigmata include *Hutchinson's teeth* -- centrally notched, widely spaced, peg-shaped upper central incisors -- and "mulberry" molars -- sixth-year molars with multiple, poorly developed cusps. The abnormal facies of patients with congenital syphilis include frontal bossing, saddle nose, and poorly developed maxillae. Saber shins, characterized by anterior tibial bowing, are rare. *Rhagades* are linear scars at the angles of the mouth and nose that are caused by secondary bacterial infection of the early facial eruption. Other stigmata include unexplained nerve deafness, old chorioretinitis, optic atrophy, and corneal opacities due to past interstitial keratitis.

## LABORATORY EXAMINATIONS

**Demonstration of the Organism** Dark-field microscopic examination of lesion exudate is useful in evaluating moist cutaneous lesions, such as the chancre of primary syphilis or the condylomata lata of secondary syphilis. The identification of a single characteristic motile organism by a trained observer is sufficient for diagnosis. Examination of oral lesions and anal ulcers by this method is not recommended, as it is difficult to differentiate *T. pallidum* from other spirochetes that may be present.

Most syphilis is diagnosed in settings where dark-field microscopy is not available. The direct fluorescent antibody *T. pallidum* (DFA-TP) test, an alternative available at central laboratories, uses fluorescein-conjugated polyclonal antitreponemal antibody for the detection of *T. pallidum* in fixed smears prepared from suspect lesions. More sensitivePCRtests have been developed but are available only in research laboratories.

*T. pallidum* can be found in tissue with appropriate silver stains, although these results should be interpreted with caution because artifacts resembling *T. pallidum* are often seen. Treponemes can be demonstrated more reliably in tissue by immunofluorescent or immunohistochemical methods using specific monoclonal or polyclonal antibodies to *T. pallidum*.

**Serologic Tests for Syphilis** There are two types of serologic tests for syphilis: nontreponemal and treponemal. Both types of tests are reactive in persons with any treponemal infection, including yaws, pinta, and endemic syphilis.

The nontreponemal tests measure IgG and IgM directed against a cardiolipin-lecithin-cholesterol antigen complex. The most widely used nontreponemal antibody tests for syphilis are the rapid plasma reagin (RPR) test, which can be automated (ART), and theVDRLslide test. In these tests, antibody is detected by the microscopic or macroscopic flocculation of the antigen suspension. The RPR test may be more expensive than the VDRL test, but it is easier to perform and uses unheated serum; it is the test of choice for rapid serologic diagnosis in a clinic or office setting. The VDRL test, however, remains the standard for use withCSF.

TheRPR andVDRLtests are equally sensitive and may be used for initial screening or for quantitation of serum antibody. The titer reflects the activity of the disease. A fourfold or greater rise in titer may be seen during the evolution of early syphilis. VDRL titers usually reach 1:32 or higher in secondary syphilis. A persistent fall of two dilutions

(fourfold) or greater following treatment of early syphilis provides essential evidence of an adequate response to therapy. VDRL titers do not correspond directly to RPR titers, and sequential quantitative testing (as for response to therapy) must employ a single test.

Two standard treponemal tests are used for confirmation of reactive nontreponemal results: the fluorescent treponemal antibody-absorbed (FTA-ABS) test and the agglutination assays for antibodies to *T. pallidum*. The microhemagglutination assay for *T. pallidum* (MHA-TP) has been replaced by the Serodia TP-PA test (Fujirebio, Tokyo), which is more sensitive for primary syphilis. The *T. pallidum* hemagglutination test (TPHA) is widely used in Europe but is not available in the United States. Both the agglutination assays and the FTA-ABS tests are very specific and, when used for confirmation of positive non-treponemal tests, have a very high positive predictive value for the diagnosis of syphilis. However, even these tests give false-positive results at rates as high as 1 to 2% when used for the screening of normal populations. New enzyme-linked immunosorbent assays have also been approved as confirmatory tests.

The relative sensitivities of theVDRLtest, theFTA-ABStest, and theMHA-TPin the various stages of untreated syphilis are shown inTable 172-1. The nontreponemal tests are nonreactive in about one-quarter of patients presenting with primary syphilis. In early primary syphilis, the detection of antibody can be maximized either by the performance of an FTA-ABS test or simply by repetition of a VDRL test after 1 to 2 weeks if the initial VDRL result is negative. All treponemal and nontreponemal tests are reactive during secondary syphilis, and a nonreactive result virtually excludes syphilis in a patient with otherwise-compatible mucocutaneous lesions. (Fewer than 1% of patients with secondary syphilis have a VDRL test that is nonreactive or weakly reactive with undiluted serum but is positive at higher serum dilutions -- the *prozone phenomenon*.) While the nontreponemal tests will become nonreactive or will be reactive in lower titers following therapy for early syphilis, the treponemal tests often remain reactive after therapy and therefore are not helpful in determining the infection status of persons with past syphilis.

For practical purposes, most clinicians need to be familiar with the three uses of serologic tests for syphilis: (1) testing of large numbers of sera for screening or diagnostic purposes (e.g., theRPR orVDRLtest), (2) quantitative measurement of the antibody titer to assess the clinical activity of syphilis or to monitor the response to therapy (e.g., the VDRL or RPR test), and (3) confirmation of the diagnosis of syphilis in a patient with a positive nontreponemal antibody test or with a suspected clinical diagnosis of syphilis (e.g., theFTA-ABStest or Serodia TP-PA).

For measurement of IgM in neonates in whom congenital syphilis is suspected, the syphilis Captia-M test (Trinity Biotech, Jamestown, NY) and the 19S IgMFTA-ABStest are available.

**False-Positive Serologic Tests for Syphilis** Because the antigen used in nontreponemal tests is found in other tissues, the tests may be reactive in persons without treponemal infection, although rarely do titers exceed 1:8 in such patients. In a population selected for screening because of clinical suspicion, history of exposure, or increased risk for sexually transmitted infections, fewer than 1% of reactive tests are

falsely positive. The modernVDRL andRPRtests are 97 to 99% specific, and false-positive reactions are now limited largely to those conditions listed inTable 172-2. False positivity is common among persons with autoimmune disorders. The prevalence of false-positive nontreponemal tests increases with advancing age; 10% of people over 70 years of age have false-positive reactions. In the patient with a false-positive nontreponemal test, syphilis is excluded by a nonreactive treponemal test.

**Evaluation for Neurosyphilis** Asymptomatic involvement of theCNS is detected by examination ofCSF for pleocytosis, increased protein concentration, andVDRLactivity. CSF abnormalities can be demonstrated in up to 40% of cases of primary or secondary syphilis and in 25% of cases of latent syphilis. In older asymptomatic seropositive individuals, the yield of lumbar puncture is relatively low. *T. pallidum* has been recovered by CSF inoculation into rabbits from up to 30% of patients with primary or secondary syphilis but rarely from those with latent syphilis. The demonstration of *T. pallidum* in CSF is often associated with other CSF abnormalities; however, organisms can be recovered from patients with otherwise-normal CSF. Before the advent of penicillin, the risk of developing clinical neurosyphilis was roughly proportional to the intensity of CSF changes in early syphilis. CSF examination is essential in the evaluation of any seropositive patient with neurologic signs and symptoms and is recommended for all patients with untreated syphilis of unknown duration or of >1 year's duration. The possibility of asymptomatic neurosyphilis in some patients with early disease is not addressed by these recommendations. Because standard therapy with penicillin G benzathine (benzathine benzylpenicillin) for early syphilis fails to result in treponemicidal levels in the CSF, some experts advise lumbar puncture in secondary and early latent syphilis, particularly in patients with HIV infection.

In short, lumbar puncture should be performed in the evaluation of latent syphilis of>1 year's duration, in suspected neurosyphilis, and in late complications other than symptomatic neurosyphilis (since asymptomatic neurosyphilis may coexist with other late complications).CSFexamination is most clearly indicated in the following situations: neurologic signs or symptoms, treatment failure, a serum reagin titer³ 1:32, HIV antibody positivity, other evidence of active syphilis (e.g., aortitis, gumma, visual or hearing changes), or plans to administer nonpenicillin therapy.

TheCSFVDRLtest is highly specific but relatively insensitive and may be nonreactive even in cases of progressive symptomatic neurosyphilis. The degree of sensitivity is highest in meningovascular syphilis and paresis and is lower in asymptomatic neurosyphilis and tabes dorsalis. The unabsorbed FTA test on CSF is reactive far more often than the CSF VDRL test in all stages of syphilis, but FTA reactivity may reflect passive transfer of serum antibody into the CSF. A nonreactive CSF FTA test, however, may be used to rule out neurosyphilis.

**Evaluation for Syphilis in Patients Infected with HIV** Because persons at highest risk for syphilis (inner-city populations, homosexually active men, and people in many developing countries) are also at increased risk for HIV infection, these two infections frequently coexist in the same patient. There is evidence that syphilis and other genital-ulcer diseases may be important risk factors for the acquisition and transmission of HIV infection.

The manifestations of syphilis may be altered in patients with concurrent HIV infection, and multiple cases of neurologic relapse following standard therapy have been reported in HIV-infected patients. *T. pallidum* has been isolated from theCSF of several patients after therapy for early syphilis with penicillin G benzathine. A recent multicenter U.S. study of early syphilis found similar therapeutic responses in persons with and without concurrent HIV infection, although the study lacked sufficient statistical power to exclude an effect of HIV and 41% of subjects were lost to follow-up. This investigation confirmed the high rate ofCNSinvasion in early syphilis and the persistence of *T. pallidum* after standard therapy: 11 of 43 HIV-infected patients and 21 of 88 HIV-uninfected patients had *T. pallidum* detectable in CSF before therapy; 7 of the 35 patients who underwent lumbar puncture after therapy (some HIV-infected and others uninfected) still had *T. pallidum* detectable in CSF.

The frequency of unusual clinical and laboratory manifestations of syphilis among patients co-infected with HIV is unknown. Such changes may be dependent on the stage of HIV infection and the degree of immunosuppression. There is no clear evidence that the sensitivity of serologic tests for syphilis or the serologic response to therapy in the vast majority of HIV-infected patients with early syphilis differs from the corresponding findings in patients not infected with HIV. Interpretation of serologic results should be the same for the two groups.

Persons with newly diagnosed HIV infection should be tested for syphilis. Some authorities, persuaded by reports of the persistence of *T. pallidum* in theCSF of HIV-infected persons after standard penicillin benzathine therapy for early syphilis, recommend examination of CSF for evidence of neurosyphilis for all co-infected patients, regardless of the clinical stage of syphilis, with treatment for neurosyphilis if CSF abnormalities are found or if CSF examination is not performed. Others do not recommend routine CSF examination for HIV-co-infected patients with early syphilis and believe that standard therapy is sufficient. Serologic testing after treatment is important for all patients with syphilis, particularly those also infected with HIV.

## TREATMENT

**Treatment of Acquired Syphilis** Penicillin G is the drug of choice for all stages of syphilis. *T. pallidum* is killed by very low concentrations of penicillin G, although a long period of exposure to penicillin is required because of the unusually slow rate of multiplication of the organism. The efficacy of penicillin for syphilis remains undiminished after 50 years of use. Other antibiotics effective in syphilis include the tetracyclines, erythromycin, and the cephalosporins. Aminoglycosides and spectinomycin inhibit *T. pallidum* only in very large doses, and the sulfonamides and the quinolones are inactive.

Serum levels of penicillin G of$^{3}$0.03 ug/mL for at least 7 days are considered necessary for the cure of early syphilis. Recurrence rates for a given regimen increase as infection progresses from incubating to seronegative primary to seropositive primary to secondary to late syphilis. Therefore, it is probable, but unproven, that a longer duration of therapy is required to effect cure as the infection progresses. For these reasons, some authorities use more prolonged penicillin therapy than that recommended by the U.S. Public Health Service when treating secondary, latent, or late syphilis.

The treatment regimens recommended for syphilis are summarized in Table 172-3 and are discussed below.

***Early Syphilis*** Preventive (abortive, "epidemiologic") treatment is recommended for seronegative individuals without signs of syphilis who have been exposed to infectious syphilis within the previous 3 months. Before treatment is given, every effort should be made to establish a diagnosis by examination and serologic testing. *The regimens recommended for prevention are the same as those recommended for early syphilis*.

Penicillin G benzathine is the most widely used agent for the treatment of early syphilis (including primary, secondary, and early latent syphilis), although it is more painful on injection than penicillin G procaine. A single dose of 2.4 million units cures more than 95% of cases of primary syphilis. Because the drug's efficacy in secondary syphilis may be slightly lower, some physicians administer a second dose of 2.4 million units 1 week after the initial dose at this stage of disease. Clinical relapse can follow treatment with penicillin G benzathine in patients with both HIV infection and early syphilis. Because the risk of neurorelapse may be higher in HIV-infected patients, examination ofCSF from HIV-seropositive individuals with syphilis of any stage is recommended by some experts; therapy appropriate for neurosyphilis should be given if there is any evidence ofCNSsyphilis.

For penicillin-allergic patients with early syphilis, a 2-week course of therapy with doxycycline or tetracycline is recommended. These regimens appear to be effective, although no well-controlled studies have been performed and poor compliance may be problematic. Although ceftriaxone and azithromycin have shown activity against *T. pallidum* in animals, human trials have not been of sufficient scope to permit the recommendation of either drug for any stage of syphilis.

***Late latent and late syphilis (normal CSF)*** IfCSFabnormalities are found, the patient should be treated for neurosyphilis. The recommended treatment for late latent syphilis with normal CSF, for cardiovascular syphilis, and for late benign syphilis (gumma) is penicillin G benzathine, 2.4 million units intramuscularly once a week for 3 successive weeks (7.2 million units total). Doxycycline or tetracycline (given for 1 month) offers an untested alternative for penicillin-allergic patients with latent or late syphilis and normal CSF. The clinical response to treatment for benign tertiary syphilis is usually impressive; however, responses to therapy for cardiovascular syphilis are not dramatic because aortic aneurysm and aortic regurgitation cannot be reversed by antibiotic treatment.

***Neurosyphilis*** The 1998 neurosyphilis treatment guidelines of the Centers for Disease Control and Prevention (CDC) are presented inTable 172-3. Penicillin G benzathine, given in total doses of up to 7.2 million units to adults or 50,000 units per kilogram to infants, does not produce detectable concentrations of penicillin G inCSF, and asymptomatic neurosyphilis may relapse in patients treated with 2.4 million units; the risk may be higher in HIV-infected patients. Therefore, the use of penicillin G benzathine alone for the treatment of neurosyphilis is not recommended. On the other hand, administration of intravenous penicillin G in doses of ³12 million units per day for 10 days or longer is thought to ensure treponemicidal concentrations of penicillin G in CSF and occasionally cures infection in patients who fail to respond to other therapy. The

clinical response to penicillin therapy for meningeal syphilis is dramatic, but the response to treatment for parenchymal neurosyphilis is variable. In general, treatment of neurosyphilis in which damage has already been done may produce no clinical change but may arrest disease progression.

Several recent publications have reported neurologic relapse after high-dose intravenous penicillin therapy for neurosyphilis in HIV-infected patients. No alternative therapies have been explored, but careful follow-up is essential, and re-treatment is warranted in such patients.

No data support the use of antibiotics other than penicillin G for the treatment of neurosyphilis; however, some of the third-generation cephalosporins may deserve further evaluation. In patients with penicillin allergy demonstrated by skin testing, desensitization may be the best course (Chap. 126).

***Management of Syphilis in Pregnancy*** Every pregnant woman should undergo a nontreponemal test at her first prenatal visit, and women at high risk of exposure should have a repeat test in the third trimester and at delivery. In the pregnant patient with presumed syphilis (evidenced by a reactive serology, with or without clinical manifestations) and with no history of treatment for syphilis, expeditious evaluation and initiation of treatment are essential. Therapy should be administered according to the stage of the disease, as for nonpregnant patients. Patients should be warned of the risk of a Jarisch-Herxheimer reaction, which may be associated with mild premature contractions but rarely results in premature delivery.

Penicillin is the only recommended therapy for syphilis in pregnancy. If the patient has a well-documented penicillin allergy, desensitization and penicillin treatment should be undertaken in a hospital according to the 1998 sexually transmitted diseases treatment guidelines issued by theCDC. After treatment, a quantitative nontreponemal test should be repeated monthly throughout pregnancy. Treated women whose titers rise fourfold or who do not show a fourfold decrease in titer in a 3-month period should be re-treated.

**Evaluation and Management of Congenital Syphilis** Newborn infants of mothers with reactiveVDRL orFTA-ABStests may themselves have reactive tests, whether or not they have become infected, because of transplacental transfer of maternal IgG antibody. Rising or persistent titers indicate infection, and the infant should be treated. Neonatal IgM antibody can be detected in cord or neonatal serum with the syphilis Captia-M or 19S IgM FTA-ABS test. Alternatively, monthly quantitative nontreponemal tests may be performed on asymptomatic infants born to women treated adequately with penicillin during pregnancy.

*An infant should be treated at birth* if the seropositive mother has received penicillin therapy in the third trimester, inadequate penicillin treatment, or therapy with a drug other than penicillin; if her treatment status is unknown; or if the infant may be difficult to follow. It is unwise to require proof of diagnosis before treatment in such cases. TheCSFshould be examined to obtain baseline values before treatment. Penicillin is the only recommended drug for syphilis in infants. The penicillin dosage used for the treatment of the patient with late congenital syphilis is calculated in the same way as for the infant, until dosage based on weight reaches that used for adult neurosyphilis.

Specific recommendations for the treatment of infants are included in theCDC's 1998 guidelines.

**Jarisch-Herxheimer Reaction** A dramatic though usually mild reaction consisting of fever (average temperature elevation, 1.5°C), chills, myalgias, headache, tachycardia, increased respiratory rate, increased circulating neutrophil count, and vasodilation with mild hypotension may follow the initiation of treatment for syphilis. This reaction occurs in approximately 50% of patients with primary syphilis, 90% of those with secondary syphilis, and 25% of those with early latent syphilis. The onset comes within 2 h of treatment, the temperature peaks at about 7 h, and defervescence takes place within 12 to 24 h. The reaction is more delayed in neurosyphilis, with fever peaking after 12 to 14 h. In patients with secondary syphilis, erythema and edema of the mucocutaneous lesions increase; occasionally, subclinical or early mucocutaneous lesions may first become apparent during the reaction. The pathogenesis of this reaction is undefined, although recent studies have demonstrated the induction of inflammatory mediators such as tumor necrosis factor by treponemal lipoproteins. Patients should be warned to expect such symptoms, which can be managed by bed rest and aspirin. Steroid and other anti-inflammatory therapy is not required for this mild transient reaction.

**Follow-Up Evaluation of Responses to Therapy** The response of early syphilis to treatment should be determined by monitoring of the quantitativeVDRL orRPRtiter 1, 3, 6, and 12 months after treatment. More frequent serologic examination (1, 2, 3, 6, 9, and 12 months) is recommended for patients concurrently infected with HIV. Because theFTA-ABSand agglutination tests remain positive in most patients treated for seropositive syphilis, these tests are not useful in following the response to therapy. After successful treatment of seropositive first-episode primary or secondary syphilis, the VDRL titer progressively declines, becoming negative by 12 months in 40 to 75% of seropositive primary cases and in 20 to 40% of secondary cases. Patients with a history of syphilis have less rapid declines in titer and are less likely to become VDRL- or RPR-negative. If the VDRL test becomes negative or if VDRL titers drop to a fixed low value within 1 or 2 years, lumbar puncture is unnecessary since theCSFexamination is almost invariably normal and there is little risk of subsequent neurosyphilis. However, if a VDRL titer ³1:8 fails to fall by at least fourfold within 12 months, if the VDRL titer rises by fourfold, or if clinical symptoms persist or recur, re-treatment is indicated. Every effort should be made to differentiate treatment failure from reinfection, and the CSF should be examined. Patients in whom treatment failure is suspected, especially those with abnormal CSF, should be treated for neurosyphilis. If the patient remains seropositive but asymptomatic after such re-treatment, no further therapy is necessary. Patients treated for late latent syphilis frequently have low initial VDRL titers and may not have a fourfold drop after therapy with penicillin; about half of these patients remain seropositive (with low titers) for years after therapy. Re-treatment is not warranted unless the titer rises or signs and symptoms of syphilis appear.

The activity of neurosyphilis correlates best with the degree ofCSFpleocytosis, and this measure provides the most sensitive index of response to treatment. CSF should be examined every 6 months for 3 years after the treatment of asymptomatic or symptomatic neurosyphilis or until CSF findings return to normal. An elevated CSF cell count falls to£10/uL in 3 to 12 months in 95% of adequately treated cases and becomes normal in all cases within 2 to 4 years. Elevated levels of CSF protein fall more slowly,

and the CSF VDRL titer declines gradually over a period of several years.

**Persistence of *T. pallidum*** The persistence of *T. pallidum* in the aqueous humor,CSF, lymph nodes, brain, inflamed temporal arteries, and other tissues after "adequate" penicillin treatment has been suggested by dark-field microscopy, immunofluorescent antibody and silver staining techniques, rabbit inoculation, and PCR. Because the data on persisting treponemes are scanty, no modification of the treatment recommendations seems warranted for HIV-uninfected persons. Adherence to recommendations regarding CSF examination before the selection of therapy should minimize the possibility that *T. pallidum* will persist in the CSF.

## IMMUNITY TO AND PREVENTION OF SYPHILIS

About 60% of contacts of patients with primary and secondary syphilis become infected, with lower risk in contacts exposed to early latent syphilis. The rate of development of acquired resistance to *T. pallidum* after natural or experimental infection is related to the size of the antigenic stimulus, which depends on both the size of the infecting inoculum and the duration of infection before treatment. The role of serum antibody in conferring immunity to syphilis remains controversial. Passively administered antibody prevents or delays the appearance of clinical manifestations of syphilis in the rabbit model; it does not prevent infection. Cellular immunity is considered to be of major importance in the healing of early lesions and the control of syphilitic infection. The cellular infiltration of early lesions predominantly involves T lymphocytes and macrophages. The cytokine milieu of primary and secondary lesions is of the $T_H1$ type, consistent with the clearance of organisms by activated macrophages. Specific antibody enhances phagocytosis and is required for macrophage-mediated killing of *T. pallidum*.

Inability to cultivate pathogenic treponemes in vitro has hindered the analysis of treponemal antigens. Attempts to induce immunity to syphilis by vaccination have shown limited promise, although repeated injection of rabbits withg-irradiated motile treponemes has conferred immunity to rechallenge. The outer membrane of *T. pallidum* contains few integral membrane proteins, and none has been definitively identified. Several newly described antigens of *T. pallidum*, including TprK, have induced partial immunity to challenge in the rabbit model, and syphilis vaccine development is being actively pursued.

**ACKNOWLEDGEMENT**

***The author wishes to acknowledge the substantive contributions of the former coauthor, Dr. King K. Holmes, to the content and organization of this chapter. His original framework continues to serve as the structure for this revision.***

(Bibliography omitted in Palm version)

Back to Table of Contents

## 173. ENDEMIC TREPONEMATOSES - *Sheila A. Lukehart*

The endemic, or nonvenereal, treponematoses are bacterial infections that are caused by close relatives of *Treponema pallidum* subspecies *pallidum*, the etiologic agent of venereal syphilis (Chap. 172). Yaws, pinta, and endemic syphilis are distinguished from venereal syphilis by mode of transmission, age of acquisition, geographic distribution, and clinical features. These infections are limited primarily to rural areas of developing nations and are seen in the United States and Europe only in recent immigrants from endemic regions. Much of our "knowledge" about the endemic treponematoses is based upon impressions and observations of health care workers who have visited endemic areas; virtually no well-designed studies of the natural history, diagnosis, or treatment of these infections have been conducted. A comparison of the treponemal infections is shown in Table 173-1.

### EPIDEMIOLOGY

The endemic treponematoses are chronic diseases acquired during childhood and, like syphilis, can cause severe late manifestations years after initial infection. These infections were very common in Africa, Asia, and South America when the World Health Organization (WHO) and UNICEF embarked on a highly successful mass eradication campaign. From 1952 to 1969, it is estimated that over 160 million people were examined for treponemal infections and over 50 million cases, contacts, and latent infections were treated. This categorical program is one of WHO's outstanding successes in that the prevalence of active yaws was reduced from >20% to <1% in many rural areas and endemic syphilis was eradicated in Bosnia. In the decades since the eradication programs, lack of focused surveillance and diversion of resources to other pressing needs have resulted in a resurgence of these infections in some regions, particularly in Africa. The estimated geographic distribution of the endemic treponematoses in the 1990s is shown inFig. 173-1. In the early 1980s, WHO sponsored a series of regional meetings on the endemic treponematoses, and areas of resurgent yaws morbidity were identified in West Africa (Ivory Coast, Ghana, Togo, Benin) and extending into the Central African Republic and rural Democratic Republic of Congo (formerly Zaire). The prevalence of endemic syphilis is estimated to be>10% in some regions of Mali, Niger, Burkina Faso, and Senegal. In Asia and the western Pacific, yaws is still prevalent in Indonesia, Papua New Guinea, and the Solomon Islands; cases have also been identified in Laos and Kampuchea. In the Americas, foci of yaws persist in Haiti and other Caribbean islands, Peru, Colombia, Ecuador, Brazil, Guyana, and Surinam. Pinta is limited to Central America and northern South America, where it is found rarely and only in remote villages.

### MICROBIOLOGY

The etiologic agents of the endemic treponematoses are *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (endemic syphilis), and *T. carateum* (pinta). These little-studied organisms are morphologically identical to *T. pallidum* subspecies *pallidum*, and no antigenic differences among the pathogenic treponemes have been identified to date. A controversy has existed about whether the treponematoses are caused by different organisms or by the same organism, with clinical manifestations and routes of transmission being defined by the climate of the

region and the culture of the population. Three of the four organisms have been placed in the same species because of their genetic similarity; the fourth (*T. carateum*) remains a separate species simply because no organisms have been available for genetic studies. However, a molecular signature has been defined that can be used to differentiate *T. pallidum* subspecies *pallidum* from *T. pallidum* subspecies *pertenue* and *T. pallidum* subspecies *endemicum*, and unpublished studies have identified a number of distinct differences in the *tpr* gene family between venereal and nonvenereal treponemes. Whether these differences are related to the different clinical courses has not yet been determined.

## CLINICAL FEATURES

All of the treponemal infections are characterized by defined disease stages, with a localized primary lesion, disseminated secondary lesions, periods of latency, and possible late lesions. The stages are most clearly defined in venereal syphilis, while the primary and secondary manifestations are more frequently overlapping in yaws and endemic syphilis; the late manifestations of pinta are very mild relative to the destructive lesions of the other treponematoses. The current preference is to divide the clinical course of the endemic treponematoses into "early" and "late" stages.

The major clinical features that are thought to differ between venereal syphilis and the nonvenereal infections are the lack of congenital transmission and lack of central nervous system (CNS) involvement in the nonvenereal infections. It is not known whether these distinctions are accurate. Because of the high degree of genetic relatedness among the organisms, there is little biologic reason to think that *T. pallidum* subspecies *endemicum* and *T. pallidum* subspecies *pertenue* would be unable to cross the blood-brain barrier or to invade the placenta. These organisms obviously can disseminate from the site of primary infection to other tissues, and they can persist for decades. In this respect, they are like *T. pallidum* subspecies *pallidum*. Even if invasion of the placenta or the CNS occurs in endemic treponemal infection, there are a number of reasons that these manifestations might not have been recognized. The lack of recognized congenital infection may be due to the fact that the nonvenereal treponematoses are usually acquired during childhood. The degree of spirochetemia (the presumed source of placental and fetal infection) is greatly diminished during the latent stage, and by the time an infected girl becomes sexually mature, she would be at low risk for transplacental transmission. Neurologic involvement may not have been recognized in nonvenereal treponemal infection because of the lack of trained medical personnel in endemic regions, the lag of years to decades between acquisition of infection and possible CNS manifestations, or a low rate of symptomatic CNS disease. The lack of longitudinal studies in endemic areas makes conclusions about the natural history of these infections tenuous.

Some published evidence supports congenital transmission as well as cardiovascular, ophthalmologic, andCNSinvolvement in yaws. Although the case is strong, particularly for CNS involvement, most studies that have shown a relatively high incidence (average, 24.9%) of cerebrospinal fluid (CSF) abnormalities in patients with yaws were not controlled for other possible causes of CSF abnormalities, did not include treponeme-specific tests, or did not follow patients for resolution of abnormalities after antitreponemal therapy. Thus, while no firm conclusions can be drawn about the

invasion of the CNS and placenta by the non-*pallidum* treponemes, it may be erroneous to accept unquestioningly the frequently repeated belief that these organisms fail to cause such manifestations.

**Yaws** Also known as *pian*, *framboesia*, or *bouba*, yaws is a chronic infection that is usually acquired in childhood and is caused by *T. pallidum* subspecies *pertenue*. The disease is characterized by the development of one or several primary lesions (called the "mother yaw"), followed by the appearance of multiple disseminated skin lesions. The early lesions may persist for many months, are infectious, and usually recur several times within the early years of infection. Late manifestations are destructive and can involve skin, bone, and joints.

The infection is transmitted by direct contact with infectious lesions, and transmission may be enhanced by disruption of the skin by insect bites or abrasions. Children with open lesions and without covering clothing are most likely to transmit infection during play or group sleeping. After an average incubation period estimated at 3 to 4 weeks, the first lesion begins as a papule, usually on an extremity, and then enlarges (particularly during moist warm weather) to become papillomatous or "raspberry-like" (thus the name "framboesia") (Fig. 173-2). Regional lymphadenopathy develops, and the lesion usually heals within 6 months; dissemination is thought to occur during the early weeks and months of infection. A generalized secondary eruption, accompanied by generalized lymphadenopathy, appears either concurrent with or following the primary lesion, may take several forms (macular, papular, or papillomatous), and may become secondarily infected with other bacteria. Painful papillomatous lesions on the soles of the feet result in a painful crablike gait ("crab yaws"), and periostitis may result in nocturnal bone pain and polydactylitis. All early skin lesions are infectious, and cutaneous relapses are common during the first 5 years. Late yaws is recognized in ~10% of untreated patients and is manifested by gummas of the skin and long bone, hyperkeratoses of the palms and soles, osteitis and periostitis, and hydrarthrosis. The late gummatous lesions are characteristically very destructive and extensive. Destruction of the nose, maxilla, palate, and pharynx is termed *gangosa* and is similar to the destructive lesions seen in leprosy and leishmaniasis.

**Endemic Syphilis** Endemic syphilis, also called *bejel*, *siti*, *dichuchwa*, *njovera*, or *skerljevo*, is a chronic infection caused by *T. pallidum* subspecies *endemicum*. Like other endemic treponematoses, endemic syphilis is chronic and is acquired in childhood. The early lesions are primarily localized to the mucocutaneous and mucosal surfaces, and the infection may be transmitted by direct contact or by shared drinking and eating utensils. A role for insects in transmission has been suggested but is unproved. The initial lesion often goes unrecognized, and the first noticeable lesion is usually an intraoral mucous patch or a mucocutaneous lesion resembling the condylomata lata of secondary syphilis (Fig. 173-2). This eruption may last for months or even years, and treponemes can readily be demonstrated in early lesions. Periostitis and regional lymphadenopathy are common. After a variable period of latency, late manifestations may appear, including osseous and cutaneous gummas. Destructive gummas, osteitis, and gangosa are more common in endemic syphilis than in late yaws. Gummas of the nipples develop in women who have previously had endemic syphilis and who breast-feed infants with oral lesions. Thus, it appears that the late lesion may result from repeated exposure of a sensitized host.

**Pinta** Pinta (also called *mal del pinto*, *carate*, *azul*, or *purupuru*) is the most benign of the treponemal infections and is caused by *T. carateum*. This disease has three stages that are characterized by marked changes in skin color, but it does not appear to cause destructive lesions or to involve other tissues. Transmission occurs by direct contact, usually during late childhood. The initial papule is most often located on the extremities or face and is pruritic. After one to many months of infection, numerous disseminated secondary lesions (*pintides*) appear. These lesions are initially red but become deeply pigmented, ultimately turning a dark slate blue. The secondary lesions are infectious and highly pruritic and may persist for years. Late pigmented lesions are called *dyschromic macules* and contain treponemes. Over time, most pigmented lesions show varying degrees of depigmentation, becoming brown and eventually white and giving the skin a mottled appearance. The white achromic lesions are characteristic of the late stage.

## DIAGNOSIS

Diagnosis of the endemic treponematoses is based upon clinical manifestations and, when available, serologic testing. The same tests that are used for venereal syphilis (Chap. 172) become reactive during all treponemal infections, and there is no serologic test than can discriminate among the different infections. The nonvenereal treponemal infections should be considered in the evaluation of a reactive syphilis serology in any person who has immigrated from an endemic area.

## TREATMENT

The recommended therapy for patients and their contacts is benzathine penicillin at a dose of 1.2 million units intramuscularly; that for children under 10 years of age is 600,000 units. This is half the dose recommended for patients and contacts with early venereal syphilis. There have been no controlled studies to show that the lower dose is effective in stopping relapse or progression to late disease. Definitive evidence of resistance to penicillin is lacking. However, because failure to heal existing lesions and frequent relapse following treatment for yaws have been described in Papua New Guinea, some health workers have suggested doubling the recommended dose of benzathine penicillin. Solely on the basis of experience with venereal syphilis, it is thought that doxycycline, tetracycline, and erythromycin (at doses appropriate for syphilis;Chap. 172) are therapeutic alternatives for patients allergic to penicillin. A Jarisch-Herxheimer reaction (Chap. 172) may follow treatment of endemic treponematoses.

## CONTROL

The endemic treponematoses can be controlled with inexpensive therapy. However, the often-remote locations of the affected populations limit availability of medical care. Although the mass treatment programs of three decades ago were widely successful, time has shown that sustained control requires vigilance in regular screening and in the investigation of outbreaks -- luxuries that are often impossible in countries with more pressing medical needs. There is concern that, as HIV spreads throughout developing countries, it may markedly affect the manifestations and transmission of the endemic

treponematoses.

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(Bibliography omitted in Palm version)

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Back to Table of Contents

## 174. LEPTOSPIROSIS - *Peter Speelman*

Leptospirosis is an infectious disease caused by pathogenic leptospires and characterized by a broad spectrum of clinical manifestations, varying from inapparent infection to fulminant, fatal disease. In its mild form, leptospirosis may present as an influenza-like illness with headache and myalgias. Severe leptospirosis, characterized by jaundice, renal dysfunction, and hemorrhagic diathesis, is referred to as *Weil's syndrome*.

### ETIOLOGIC AGENTS

Leptospires are spirochetes belonging to the order Spirochaetales and the family Leptospiraceae. Traditionally, the genus *Leptospira* comprised two species: the pathogenic *L. interrogans* and the free-living *L. biflexa*. Although seven species of pathogenic leptospires are now recognized on the basis of their DNA relatedness, it is more practical clinically and epidemiologically to use a classification based on serologic differences. The pathogenic leptospires are divided into serovars according to their antigenic composition. More than 200 serovars make up the 23 serogroups.

Leptospires are coiled, thin, highly motile organisms with hooked ends and two periplasmic flagella that permit burrowing into tissue. These organisms are 6 to 20 um long and about 0.1 um wide; they stain poorly but can be seen microscopically by dark-field examination and after silver impregnation staining. Leptospires require special media and conditions for growth; it may take weeks for cultures to become positive.

### EPIDEMIOLOGY

Leptospirosis is a zoonosis with a worldwide distribution that affects at least 160 mammalian species. Rodents, especially rats, are the most important reservoir, although other wild mammals, dogs, fish, and birds may also harbor these microorganisms. Leptospires establish a symbiotic relationship with their host and can persist in the renal tubules for years. Some serovars are associated with particular animals -- e.g., icterohaemorrhagiae/copenhageni with rats, grippotyphosa with voles, hardjo with cattle, canicola with dogs, and pomona with pigs.

Transmission of leptospires may follow direct contact with urine, blood, or tissue from an infected animal or exposure to a contaminated environment; human-to-human transmission is rare. Since leptospires are excreted in the urine and can survive in water for many months, water is an important vehicle in their transmission. Epidemics of leptospirosis may result from exposure to flood waters contaminated by urine from infected animals, as has been reported from Nicaragua. Leptospirosis occurs most commonly in the tropics because the climate as well as the sometimes poor working and hygienic conditions favor the pathogen's survival.

Humans are not commonly infected with leptospires. However, in the United States, the 40 to 120 cases reported annually to the Centers for Disease Control and Prevention certainly represent a significant underestimation of the total number. Certain occupational groups are at especially high risk; included are veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and workers in the fishing

industry. Such individuals may acquire leptospirosis through direct exposure to or contact with contaminated water and soil. Leptospirosis has also been recognized in deteriorating inner cities where rat populations are expanding. One report described leptospirosis in urban residents of Baltimore who were sporadically exposed to rat urine.

In western countries, recreational exposure and domestic animal contact are also prominent sources of leptospirosis. Recreational water activities, such as canoeing, windsurfing, swimming, and waterskiing, place persons at risk for leptospirosis. Sometimes the infection is acquired during travel abroad. In a recent study in the Netherlands, 14% of patients with confirmed leptospirosis had acquired the infection while traveling in tropical countries, mostly in Southeast Asia. Transmission via laboratory accidents has been reported but is rare. Occasionally, leptospirosis develops after unanticipated immersion in contaminated water (e.g., in an automobile accident). Most cases occur in men, with a peak incidence during the summer and fall in western countries and during the rainy season in the tropics.

## PATHOGENESIS

The pathogenesis of leptospirosis is incompletely understood. Leptospires may enter the host through abrasions in the skin or through intact mucous membranes, especially the conjunctiva and the lining of the oro- and nasopharynx. Drinking of contaminated water may introduce leptospires through the mouth, throat, or esophagus. After entry of the organisms, leptospiremia develops, with subsequent spread to all organs. Multiplication takes place in blood and in tissues, and leptospires can be isolated from blood and cerebrospinal fluid (CSF) during the first 4 to 10 days of illness. It is not clear why the presence of leptospires in the CSF does not cause damage. All forms of leptospires can damage the wall of small blood vessels; this damage leads to vasculitis with leakage and extravasation of cells, including hemorrhages. The most important known pathogenic properties of leptospires are adhesion to cell surfaces and cellular toxicity.

Vasculitis is responsible for the most important manifestations of the disease. Although leptospires mainly infect the kidneys and liver, any organ may be affected. In the kidney, leptospires migrate to the interstitium, renal tubules, and tubular lumen, causing interstitial nephritis and tubular necrosis. Hypovolemia due to dehydration or altered capillary permeability may contribute to the development of renal failure. In the liver, centrilobular necrosis with proliferation of Kupffer cells may be found. However, severe hepatocellular necrosis is not a feature of leptospirosis. Pulmonary involvement is the result of hemorrhage and not of inflammation. Invasion of skeletal muscle by leptospires results in swelling, vacuolation of the myofibrils, and focal necrosis. In severe leptospirosis, vasculitis may ultimately impair the microcirculation and increase capillary permeability, resulting in fluid leakage and hypovolemia.

When antibodies are formed, leptospires are eliminated from all sites in the host except the eye, the proximal renal tubules, and perhaps the brain, where they may persist for weeks or months. The persistence of leptospires in the aqueous humor occasionally causes chronic or recurrent uveitis. The systemic immune response is effective in eliminating the organism but may also produce symptomatic inflammatory reactions. A rise in antibody titer coincides with the development of meningitis; this association

suggests that an immunologic mechanism is responsible.

After the start of antimicrobial treatment for leptospirosis, a Jarisch-Herxheimer reaction similar to that seen in other spirochetal diseases may develop. Although frequently described in older publications, this reaction seems to be a rare event in leptospirosis and is certainly less frequent in this infection than in other spirochetal diseases.

## CLINICAL MANIFESTATIONS

It is important to try to obtain a history of exposure to contaminated materials. Serologic evidence of past inapparent infection is found in 15 to 40% of persons who have been exposed but have not become ill. In symptomatic cases of leptospirosis, clinical manifestations vary from mild to serious or even fatal. More than 90% of symptomatic persons have the relatively mild and usually anicteric form of leptospirosis, with or without meningitis. Severe leptospirosis with profound jaundice (Weil's syndrome) develops in 5 to 10% of infected individuals.

The incubation period is usually 1 to 2 weeks but ranges from 2 to 26 days. Typically, an acute leptospiremic phase is followed by an immune leptospiruric phase. The distinction between the first and second phases is not always clear, and milder cases do not always include the second phase.

**Anicteric Leptospirosis** Leptospirosis may present as an acute influenza-like illness, with fever, chills, severe headache, nausea, vomiting, and myalgias. Muscle pain, which especially affects the calves, back, and abdomen, is an important feature of leptospiral infection. Less common features include sore throat and rash. The patient usually has an intense headache (frontal or retroorbital) and sometimes develops photophobia. Mental confusion may be evident. Pulmonary involvement, manifested in most cases by cough and chest pain and in a few cases by hemoptysis, is not uncommon.

The most common finding on physical examination is fever with conjunctival suffusion. Less common findings include muscle tenderness, lymphadenopathy, pharyngeal injection, rash, hepatomegaly, and splenomegaly. The rash may be macular, maculopapular, erythematous, urticarial, or hemorrhagic. Mild jaundice may be present.

Most patients become asymptomatic within 1 week. After an interval of 1 to 3 days, the illness recurs in a number of cases. The start of this second (immune) phase coincides with the development of antibodies. Symptoms are more variable than during the first (leptospiremic) phase. Usually the symptoms last for only a few days, but occasionally they persist for weeks. Often the fever is less pronounced and the myalgias are less severe than in the leptospiremic phase. An important event during the immune phase is the development of aseptic meningitis. Although no more than 15% of all patients have symptoms and signs of meningitis, many patients may haveCSFpleocytosis. Meningeal symptoms usually disappear within a few days but may persist for weeks. Similarly, pleocytosis generally disappears within 2 weeks but occasionally persists for months. Iritis, iridocyclitis, and chorioretinitis -- late complications that may persist for years -- can become apparent as early as the third week but often present several months after the initial illness. One epidemic of uveitis among patients with leptospirosis has been reported.

**Severe Leptospirosis (Weil's Syndrome)** Weil's syndrome, the most severe form of leptospirosis, is characterized by jaundice, renal dysfunction, hemorrhagic diathesis, and high mortality. This syndrome is frequently but not exclusively associated with infection due to serovar icterohaemorrhagiae/copenhageni. The onset of illness is no different from that of less severe leptospirosis; however, after 4 to 9 days, jaundice as well as renal and vascular dysfunction generally develop. Although some degree of defervescence may be noted after the first week of illness, a biphasic disease pattern like that seen in anicteric leptospirosis is lacking. The jaundice of Weil's syndrome, which can be profound and give an orange cast to the skin, is usually not associated with severe hepatic necrosis. Death is rarely due to liver failure. Hepatomegaly and tenderness in the right upper quadrant are usually detected. Splenomegaly is found in 20% of cases.

Renal failure may develop, often during the second week of illness. Hypovolemia and decreased renal perfusion contribute to the development of acute tubular necrosis with oliguria or anuria. Dialysis is sometimes required, although a fair number of cases can be managed without dialysis. Renal function may be completely regained.

Pulmonary involvement occurs frequently, resulting in cough, dyspnea, chest pain, and blood-stained sputum, and sometimes in hemoptysis or even respiratory failure. Hemorrhagic manifestations are seen in Weil's syndrome: epistaxis, petechiae, purpura, and ecchymoses are found commonly, while severe gastrointestinal bleeding and adrenal or subarachnoid hemorrhage are detected rarely.

Rhabdomyolysis, hemolysis, myocarditis, pericarditis, congestive heart failure, cardiogenic shock, adult respiratory distress syndrome, and multiorgan failure have all been described during severe leptospirosis.

## LABORATORY AND RADIOLOGIC FINDINGS

The kidneys are invariably involved in leptospirosis (Fig. 174-CD1). Related findings range from urinary sediment changes (leukocytes, erythrocytes, and hyaline or granular casts) and mild proteinuria in anicteric leptospirosis to renal failure and azotemia in severe disease.

The erythrocyte sedimentation rate is usually elevated. In anicteric leptospirosis, peripheral leukocyte counts range from 3000 to 26,000/uL, with a left shift; in Weil's syndrome, leukocytosis is often marked. Mild thrombocytopenia occurs in up to 50% of patients and is associated with renal failure.

In contrast to patients with acute viral hepatitis, those with leptospirosis typically have elevated serum levels of bilirubin and alkaline phosphatase as well as mild increases (up to 200 U/L) in serum levels of aminotransferases. In Weil's syndrome, the prothrombin time may be prolonged but can be corrected with vitamin K. Levels of creatine phosphokinase, which are elevated in up to 50% of patients with leptospirosis during the first week of illness, may help to differentiate this infection from viral hepatitis.

When a meningeal reaction develops, polymorphonuclear leukocytes predominate

initially and the number of mononuclear cells increases later. The protein concentration in theCSF may be elevated; CSF glucose levels are normal.

In severe leptospirosis, pulmonary radiographic abnormalities are more common than would be expected on the basis of physical examination. These abnormalities most frequently develop 3 to 9 days after the onset of illness. The most common radiographic finding is a patchy alveolar pattern that corresponds to scattered alveolar hemorrhage. Radiographic abnormalities most often affect the lower lobes in the periphery of the lung fields.

**DIAGNOSIS**

A definite diagnosis of leptospirosis is based either on isolation of the organism from the patient or on seroconversion or a rise in antibody titer in the microscopic agglutination test (MAT). For a presumptive diagnosis of leptospirosis, an antibody titer of ³1:100 in the MAT or a positive macroscopic slide agglutination test in the presence of a compatible clinical illness is required. Antibodies generally do not reach detectable levels until the second week of illness. The antibody response can be affected by early treatment.

The macroscopic slide agglutination test with killed antigen is useful for screening but is not specific. TheMAT, which uses a battery of live leptospiral strains, and the enzyme-linked immunosorbent assay (ELISA), which uses a broadly reacting antigen, are the standard serologic procedures. These tests usually are available only in specialized laboratories and are used for the determination of the antibody titer and for the tentative identification of the serovar involved (thus the importance of using antigens representative of the serovars prevalent in the particular geographic area). Since cross-reactions occur frequently, however, it is often impossible to identify the infecting serovar. Serologic testing cannot be used as the basis for a decision about whether to start treatment.

In addition to theMAT and theELISA, various other tests with diagnostic value have been developed. Some tests, such as an indirect hemagglutination test, a microcapsule agglutination test, and an IgM ELISA, are commercially available. Dot-ELISA, gold immunoblot, and polymerase chain reaction techniques have been developed but are not yet used for routine diagnosis.

Leptospires can be isolated from blood and/orCSFduring the first 10 days of illness and from urine for several weeks beginning at around 1 week. Cultures may become positive after 2 to 4 weeks, with a range of 1 week to 4 months. Sometimes urine cultures remain positive for months or years after the start of illness. For isolation of leptospires from body fluids or tissues, Ellinghausen-McCullough-Johnson-Harris (EMJH) medium is useful; other possibilities are Fletcher medium and Korthoff medium. Specimens can be mailed to a reference laboratory for culture, since leptospires remain viable in anticoagulated blood (heparin, EDTA, or citrate) for up to 11 days. Isolation of leptospires is important since it is the only way the infecting serovar can be correctly identified. Dark-field examination of blood or urine frequently results in misdiagnosis and should not be used.

## DIFFERENTIAL DIAGNOSIS

Leptospirosis should be differentiated from other febrile illnesses associated with headache and muscle pain, such as malaria, enteric fever, viral hepatitis, dengue, *Hantavirus* infections, and rickettsial diseases. In light of the strong similarity in epidemiology and clinical presentation between leptospirosis and *Hantavirus* infections and given the reported occurrence of dual infections, it is advisable to conduct serologic testing for *Hantavirus* in cases of suspected leptospirosis. When patients have a flulike disease with disproportionately severe myalgia or aseptic meningitis, a diagnosis of leptospirosis should be considered.

## TREATMENT

The effectiveness of antimicrobial therapy for the mild febrile form of leptospirosis is controversial, but such treatment is indicated for more severe forms. Treatment should be initiated as early as possible; nevertheless, contrary to previous reports, treatment started after the first 4 days of illness is effective.

For severe cases of leptospirosis, intravenous administration of penicillin G, amoxicillin, ampicillin, or erythromycin is recommended (Table 174-1). In milder cases, oral treatment with tetracycline, doxycycline, ampicillin, or amoxicillin should be considered. Although several other antibiotics, including newer cephalosporins, are highly active against leptospires in vitro, no clinical experience has yet been gained with these drugs.

In rare cases, a Jarisch-Herxheimer reaction develops within hours after the start of antimicrobial therapy (see "Pathogenesis" above). Although so far the only effective mode of management is supportive, the role of antibodies to tumor necrosis factor in the treatment of this reaction deserves further study. A beneficial effect of the use of such antibodies for the modulation of the reaction has been demonstrated in patients with louse-borne relapsing fever. Patients with severe leptospirosis and renal failure may require dialysis. Those with Weil's syndrome may need transfusions of whole blood and/or platelets. Intensive care may be necessary.

## PROGNOSIS

Most patients with leptospirosis recover. Mortality is highest among patients who are elderly and those who have Weil's syndrome. Leptospirosis during pregnancy is associated with high fetal mortality. Long-term follow-up of patients with renal failure and hepatic dysfunction has documented good recovery of renal and hepatic function.

## PREVENTION

Individuals who may be exposed to leptospires through their occupations or their involvement in recreational water activities should be informed about the risks. Measures for controlling leptospirosis include avoidance of exposure to urine and tissues from infected animals, vaccination of animals, and rodent control. The animal vaccine used in a given area should contain the serovars known to be present in that area. Unfortunately, some vaccinated animals still excrete leptospires in their urine. Vaccination of humans against a specific serovar prevalent in an area has been

undertaken in some European and Asian countries and has proved effective. Chemoprophylaxis with doxycycline (200 mg once a week) has appeared to be efficacious in military personnel but is indicated only in rare instances of sustained short-term exposure.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 175. RELAPSING FEVER - *David T. Dennis*, *Grant L. Campbell*

### DEFINITION

The term *relapsing fever* describes two distinct borrelial disease entities: louse-borne relapsing fever (LBRF) and tick-borne relapsing fever (TBRF). Both are characterized by recurrent acute episodes of spirochetemia and fever alternating with spirochetal clearance and apyrexia.

### ETIOLOGY

The worldwide distribution of relapsing spirochetal fevers was recognized in the early part of the twentieth century, and the causative agents were shown to be transmitted by lice and ticks. *Borrelia recurrentis* was identified as the cause ofLBRF; differing strains of borreliae causingTBRFwere usually named according to the species of *Ornithodoros* tick responsible for their transmission (Table 175-1). Sequencing of both flagellin and 16S ribosomal RNA genes reveals homogeneity among LBRF strains and considerable heterogeneity between Old World and New World TBRF strains.

Relapsing-fever borreliae are gram-negative bacteria that belong to the family Spirochaetaceae. They are helical in shape and average 0.2 to 0.5 um in width and 5 to 20 um in length. They comprise an outer membrane, an intermediate peptidoglycan layer, and an inner cytoplasmic membrane, which encloses the protoplasmic cylinder. Periplasmic flagella (variable numbers have been described) are situated beneath the outer membrane. Relapsing-fever borreliae are slow-growing and microaerophilic; they grow best at 30 to 35°C. BothTBRF andLBRFspirochetes grow well in Barbour-Stoenner-Kelly (BSK II) medium.

Relapsing-fever borreliae are distinguished by remarkable antigenic variability and strain heterogeneity. New *Borrelia* serotypes spontaneously emerge at a high rate, resulting from a unique process of DNA rearrangement within genes located on linear plasmids. These genes code for variable major proteins (VMPs) found on the spirochete's outer-membrane surface. This antigenic variation, generated by sequential expression of previously silent *vmp* genes for serotype-specific VMPs, allows the borreliae to escape the immune response of the host and results in the relapse phenomenon characteristic of infection with these organisms. Borrelial *vmp* gene expression also varies between mammalian and arthropod hosts.

### EPIDEMIOLOGY

**Louse-Borne Relapsing Fever** Body lice (*Pediculus humanus* var. *corporis*) become infected with *B. recurrentis* by feeding on spirochetemic humans, the only reservoirs of infection. In lice, *B. recurrentis* spirochetes are found almost exclusively in the hemolymph; humans acquire infection when infected body lice are crushed and their fluids contaminate mucous membranes or breaks in the skin (such as abrasions caused by scratching of pruritic louse bites). Spirochetes are not transmitted directly by the bite of a louse (anterior station transmission) or by inoculation of louse feces (posterior station transmission). Lice have a life span of only a few weeks, feed at frequent intervals, and survive only a few days off the human host.

LBRFhas severely affected military and civilian populations disrupted by war and other disasters. During the Industrial Revolution, the disease was common among slum dwellers, prisoners, and others living in impoverished, overcrowded, and unhygienic conditions. In the first half of the twentieth century, during periods of war and famine, both LBRF and louse-borne typhus were epidemic in eastern Europe, the Balkans, and the former Soviet Union. LBRF has disappeared from its former global range as improvements have been made in standards of living, sanitation, and hygiene; it is now an important disease only in northeastern Africa, especially the highlands of Ethiopia, where an estimated 10,000 cases occur annually. In Ethiopia, the disease affects mostly homeless men crowded together in unhygienic circumstances, especially during the cool rainy season, when it is more difficult for them to change and wash their clothing. LBRF has repeatedly spilled out of Ethiopia into neighboring Somalia and Sudan, especially affecting displaced persons. LBRF does not pose a significant risk to tourists or other casual visitors but can be acquired from lice by persons (such as relief workers) in intimate contact with those affected as well as through accidental needle stick or mucocutaneous contact with infected blood.

**Tick-Borne Relapsing Fever** Soft ticks (Argasidae, *Ornithodoros* spp.) transmitTBRF. The ticks become infected by feeding on spirochetemic hosts. Except for *B. duttoni* (a prominent cause of TBRF in sub-Saharan Africa), TBRF borreliae are zoonotic disease agents found naturally in rodents (rats, mice, chipmunks, and squirrels) and in lagomorphs (rabbits and hares). The spirochetes are transmitted by ticks to humans and animals via saliva and excretory fluids when the tick feeds. Infection in ticks is transmitted vertically from one stage to the next; in some species, infection is transmitted transovarially over several generations. Soft ticks are hardy and can survive for 10 years or more with only an occasional blood meal. These ticks feed painlessly, relatively quickly (for 20 to 45 min), and usually at night while hosts are sleeping. Thus patients with TBRF are often unaware of tick exposures.

TBRFborreliae are widely distributed throughout the world. Human infection with these organisms is generally underrecognized and underreported. TBRF is most highly endemic in sub-Saharan Africa but is also found in countries of the Mediterranean littoral, Middle Eastern states, southern Russia, the Indian subcontinent, and China. In the United States, this disease occurs west of the Mississippi River, especially in mountainous areas, where *B. hermsii* is the causative agent. TBRF is reported at low frequency throughout Latin America. The disease typically occurs sporadically or in small -- often familial -- clusters. Infected soft ticks may cause repeated infections among persons living or sleeping in the same dwelling. In sub-Saharan Africa, *O. moubata*, the vector of *B. duttoni*, infests native huts and rest houses, hiding in crevices of floors and walls during the day and emerging at night to feed on sleeping inhabitants. In the United States, *B. hermsii* infections most often occur during spring and summer months among persons sleeping in rustic mountain cabins. Infections of humans are sometimes precipitated by the disappearance of rodents (e.g., as a result of epizootic plague) that nest in foundations, wall spaces, and attics and that serve as the usual maintenance hosts for *O. hermsi* ticks. Outbreaks caused by *B. hermsii* have taken place among persons staying in cabins along the north rim of the Grand Canyon and in the mountains of California, Idaho, and Colorado. Rodent-infested caves in southwestern states are associated with occasional cases of relapsing fever caused by

*B. turicatae*.

## PATHOGENESIS AND PATHOLOGY

In humans, relapsing-fever borreliae penetrate the skin or mucous membranes, multiply in the blood, and circulate in great numbers during febrile periods. The organisms also may be found in the liver, spleen, central nervous system, bone marrow, and other tissues and may be sequestered at these sites during periods of remission. The severity of disease is positively related to spirochete density in the blood. Even though the pathophysiologic manifestations of the disease resemble responses to endotoxin, and although plasma from some patients with relapsing fever coagulates *Limulus* amebocyte lysates, borreliae and other spirochetes have not been shown to express a true lipopolysaccharide (endotoxin) molecule. Infection with *B. recurrentis* does, however, activate protein mediators of inflammation, such as Hageman factor, prekallikrein, and proteins of the complement system; furthermore, a spirochetal heat-stable pyrogenic factor stimulates mononuclear phagocytes to express increased amounts of leukocyte pyrogen and thromboplastin.

The Jarisch-Herxheimer reaction in patients withLBRF is associated with a release of various cytokines into the plasma, including interleukin 6, interleukin 8, C-reactive protein, and enormous amounts of tumor necrosis factor a (TNF-a). Pretreatment of LBRF patients with antibody to TNF-asuppresses the Jarisch-Herxheimer reactions that follow penicillin treatment and reduces the plasma concentrations of certain other cytokines.

Findings at autopsy of patients with relapsing fever most often include hepatosplenomegaly and variable edema and swelling of other organs, such as the brain, lungs, and kidneys. On microscopic examination, the spleen is congested and contains multiple microabscesses composed of mononuclear cells that replace the white pulp, the myocardium displays diffuse histiocytic inflammation and interstitial edema, and the liver has areas of midzonal necrosis. Petechial hemorrhages are commonly evident over the surfaces of the meninges, pleura, heart, spleen, liver, kidneys, and mesentery. Subcapsular and parenchymal hemorrhagic infarcts of the spleen, heart, liver, and brain are sometimes grossly visible. Icterus is a common finding in severe and fatal cases of relapsing fever.

## CLINICAL MANIFESTATIONS

The clinical manifestations of LBRFand TBRFare similar. The mean incubation period is 7 days (range, 2 to 18 days), and the onset of illness is sudden, with fever, headache, shaking chills, sweats, myalgias, and arthralgias. The arthralgia of relapsing fever can be severe, involving small and large joints, but there is no evidence of arthritis. Dizziness, nausea, and vomiting are common. Sleep may be difficult and is sometimes accompanied by disturbing dreams. The patient is coherent but withdrawn, thirsty, and disinterested in food and other outside stimuli. The fever is high from the first, with a usual temperature of³40°C (³104°F); fever is most often irregular in pattern and is sometimes accompanied by delirium. Patients become progressively prostrate as the disease advances. The pulse is rapid and the patient is mildly tachypneic. Meningism may be found. The conjunctivae are often injected, and the patient usually exhibits

photophobia. The sclerae are sometimes icteric, most commonly in the later stages of illness. The mucous membranes are often dry, and the patient is usually dehydrated. Scattered petechiae develop on the trunk, extremities, and mucous membranes in one-third or more of patients with LBRF and in fewer patients with TBRF. A nonproductive cough is common, but chest sounds are usually normal; pleuritic pain and an accompanying pleuritic rub are sometimes noted. Cardiac findings are compatible with a high-output state; tachycardia and summation gallop are common. Tender enlargement of the spleen and liver frequently characterizes the acute phase of illness.

Epistaxis and blood-tinged sputum are common complications, and gastrointestinal and central nervous system hemorrhage can occur. Because of this coagulopathy, oneLBRFoutbreak in southern Sudan was thought to be viral hemorrhagic fever. Other complications of variable incidence include iridocyclitis, optic neuritis, meningitis, coma, isolated cranial-nerve palsy, pneumonitis, myocarditis, and rupture of the spleen. Infection during pregnancy can result in spontaneous abortion, stillbirth, or neonatal infection. Life-threatening complications are unusual in otherwise healthy persons given supportive care, especially if the illness is diagnosed and treated early.

Without treatment, symptoms intensify over a 2- to 7-day period (average, 5 days inLBRF and 3 days inTBRF), ending in a spontaneous crisis during which spirochetes disappear from the circulation. Treatment with one of the rapidly acting antibiotics, such as erythromycin, a tetracycline, or chloramphenicol, regularly precipitates a Jarisch-Herxheimer reaction within 1 to 4 h. The severity of this reaction is positively correlated with the density of spirochetes in the blood at the time of treatment. In the first phase of the crisis or reaction (the *chill phase*), rigors and rising fever are accompanied by an increasing metabolic rate, alveolar hyperventilation, high cardiac output, increasing peripheral vascular resistance, and decreased pulmonary arterial pressure. The body temperature commonly rises to³41°C (³105.8°F). This high fever is accompanied often by agitation and confusion and sometimes by delirium. Fever can be partially controlled by the use of a cooling blanket and ice packs and by sponging of the patient with tepid water and alcohol. The chill phase terminates after 10 to 30 min, giving way to a *flush phase* characterized by a fall in body temperature, drenching sweats, and sometimes (more commonly in LBRF) a potentially dangerous fall in systemic arterial pressure and rise in pulmonary arterial pressure. Although cardiac output is maintained at high levels, the effective circulating blood volume decreases as peripheral vascular resistance falls. Vital signs must be monitored carefully during this period of the reaction, which usually lasts£8 h. Clinical and electrocardiographic evidence of myocarditis and myocardial dysfunction includes a prolonged $QT_c$interval, a third heart sound ($S_3$), elevated central venous pressure, arterial hypotension, and pulmonary edema.

The crisis is followed by a period of exhaustion, sleep, and an uneventful recovery. Not uncommonly, in the first week of convalescence, patients experience 1 or 2 days of mild fever unassociated with detectable spirochetemia. In untreated patients, spirochetemia and symptoms may recur after a period of several days or weeks (average interval to first relapse, 9 days inLBRF and 7 days inTBRF). Only one or two relapses characteristically occur in untreated patients with LBRF, whereas as many as 10 (average, three) can occur in untreated patients with TBRF. In most cases, the illness

becomes shorter and milder and the afebrile intervals longer with each relapse. Because of the great antigenic variation among *Borrelia* strains, infection confers only partial immunity, and repeated infections of the same individual have been recorded.

Diseases that should be considered in the differential diagnosis of relapsing fever or that may complicate relapsing fever include typhus fever, typhoid, nontyphoid salmonellosis, malaria, dengue and other arboviral illnesses, tuberculosis, leptospirosis, and viral hemorrhagic fevers. In the United States, the geographic distribution of Colorado tick fever overlaps that ofTBRF, and the two diseases have similar manifestations early in their courses.

## LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis of relapsing fever is confirmed most easily by the detection of spirochetes in blood, bone marrow aspirates, or cerebrospinal fluid. Motile spirochetes can be seen when fresh blood is examined by dark-field microscopy; and fixed organisms are clearly visible in Wright-, Giemsa-, or acridine orange-stained preparations of thin or dehemoglobinized thick smears of peripheral blood or buffy-coat preparations (Fig. 175-1). Organisms are found in blood taken during periods of fever preceding the crisis; smears from³70% of patients withLBRF and from fewer patients withTBRF are positive. In reference laboratories, relapsing-fever spirochetes are cultured from blood by the inoculation of BSK II medium or by the intraperitoneal inoculation of immature laboratory mice. The detection of agglutinins against *Proteus* OX-K (Weil-Felix reaction) in convalescent-phase serum supports the diagnosis. Serum antibodies to *Borrelia* can be detected by enzyme immunoassays, but these tests are unstandardized and subject to insensitivity due to antigenic variations among strains. Serologic cross-reactions occur with other spirochetes, including *B. burgdorferi* (the agent of Lyme disease) and *Treponema pallidum*.

Other laboratory findings in relapsing fever are generally nonspecific. The leukocyte count is normal or moderately elevated, with an unremarkable cell differential. Serum bilirubin levels are generally only slightly elevated. Thrombocytopenia (mean platelet count, about 50,000/uL) is evident in patients withLBRFduring the acute phase of the illness; platelet counts rebound during early convalescence. Prothrombin and partial thromboplastin times are moderately prolonged during acute illness, as are standardized bleeding times. Fibrinogen concentrations in the blood are normal, and fibrinolysis is mild or absent. Results of the Rumpel-Leede tourniquet test are negative, despite the presence of petechiae.

## TREATMENT

Relapsing-fever borreliae are exquisitely sensitive to antibiotics. Treatment with erythromycin, a tetracycline, chloramphenicol, or penicillin produces rapid clearance of spirochetes and a remission of symptoms (Table 175-2). Although a single dose of erythromycin, a tetracycline, or chloramphenicol is highly effective in the treatment ofLBRF, less is known about the efficacy of single-dose treatment ofTBRF. Empirical treatment of TBRF for 7 days is therefore recommended to reduce the risk of persisting or relapsing borreliosis. For children<8 years of age and for pregnant women, erythromycin and penicillin are the preferred drugs.

The use of delayed-release intramuscular penicillin may prolong or delay the clearance of spirochetes and thereby attenuate the accompanying Jarisch-Herxheimer reaction, but this response is not predictable; furthermore, single-dose penicillin treatment sometimes results in relapse of spirochetemia and symptoms. Glucocorticoids and nonsteroidal anti-inflammatory agents do not prevent or significantly modify the cardiopulmonary disturbances of the Jarisch-Herxheimer reaction, although hydrocortisone and acetaminophen given at the same time as antibiotics reduce peak body temperature. Although pretreatment with antibody toTNF-amay moderate the Jarisch-Herxheimer reaction in treated patients withLBRF, its widespread use in LBRF is impractical and its use inTBRF(whose treatment is associated with a relatively mild Jarisch-Herxheimer reaction) is not warranted. Close monitoring of fluid balance, arterial and venous pressures, and myocardial function is advised in supportive management of the Jarisch-Herxheimer reaction in patients with LBRF.

The management of patients with myocardial dysfunction requires caution in the administration of intravenous fluids and, in some cases, rapid digitalization. Bleeding is not controlled by heparin, and clinical studies do not suggest that disseminated intravascular coagulopathy is important. Vitamin K and other soluble vitamins are sometimes given to counter dietary deficiencies in patients withLBRF. Because postural hypotension is often pronounced during the acute phase of relapsing fever and in the early stage of recovery, patients should be assisted when arising from bed.

UntreatedLBRF has a high case-fatality rate, especially among persons in otherwise poor health, such as those in famine-affected populations. The fatality rate among treated persons is usually <5%. In general,TBRF is a milder disease than LBRF: the spontaneous crisis and the Jarisch-Herxheimer reactions are less pronounced and the case-fatality rates are lower for TBRF than for LBRF.

**PREVENTION AND CONTROL**

LBRFcan be prevented by elimination of circumstances that promote louse infestation (crowding, poverty, homelessness, poor personal hygiene), by use of practices that eliminate or reduce numbers of body lice (washing clothes, drying clothes in direct sunlight, changing clothes at frequent intervals), and by application of acaricides. Secondary complications and the spread of infection can be prevented by early case detection and treatment of infected persons and close contacts. Historically, outbreaks of LBRF have been controlled by mass delousing. In situations like those in refugee camps, individuals, their clothes, and their bedding should be deloused with appropriate acaricides, such as 0.5% permethrin dust. Impregnation of clothing with liquid permethrin, a residual acaricide, can provide long-term protection against infestation. In outbreaks of fever that involve louse-infested populations, empirical single-dose treatment with doxycycline will be effective against typhus as well as LBRF. *B. recurrentis* has a fragile life cycle and is eradicable.

TBRFcan be prevented by the avoidance of rodent- and tick-infested dwellings and infested natural sites. Limiting rodent access to the foundations and attics of homes and vacation cabins and eliminating harborage for rodents in and around these dwellings reduce the potential for tick exposure. Rodents and rodent nests should be removed

from infested buildings and their surroundings. Tick harborages of infested buildings or other circumscribed sites, such as rodent burrows and nests in hollow logs surrounding dwellings and in rodent-infested caves, can be chemically treated by pest-control specialists using various acaricides, such as carbaryl, diazinon, chlorpyrifos, pyrethrins, and malathion. Persons who enter tick-infested sites can protect themselves by wearing clothing that denies ticks access to the skin, by applying repellents to exposed skin and to clothing, and by applying an acaricide containing permethrin to clothing. Reporting of suspected cases of relapsing fever to public health authorities is important so that an epidemiologic investigation and control measures can be initiated promptly.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 176. LYME BORRELIOSIS - *Allen C. Steere*

### DEFINITION

Lyme borreliosis, a tick-transmitted spirochetal illness, usually begins with a characteristic expanding skin lesion, erythema migrans (EM; stage 1, localized infection). After several days or weeks, the spirochete may spread hematogenously to many different sites (stage 2, disseminated infection). Possible manifestations of disseminated infection include secondary annular skin lesions, meningitis, cranial or peripheral neuritis, carditis, atrioventricular nodal block, or migratory musculoskeletal pain. Months to years later (usually after periods of latent infection), intermittent or chronic arthritis, chronic encephalopathy or polyneuropathy, or acrodermatitis may develop (stage 3, persistent infection). Most patients experience early symptoms of the illness during the summer, but the infection may not become symptomatic until it progresses to stage 2 or 3. Despite regional variations, the basic stages of the illness are similar worldwide.

### ETIOLOGIC AGENT

*Borrelia burgdorferi*, the causative agent of the disease, is a fastidious, microaerophilic bacterium. The organism contains many immunogenic proteins, including a number of differentially expressed lipoproteins, most of which are encoded by plasmid DNA. The spirochete grows best at 33°C in a complex liquid medium called Barbour, Stoenner, Kelly (BSK) medium. Culture of the organism from clinical specimens (except for biopsy samples of skin at sites ofEM or acrodermatitis) has been difficult. Three groups of pathogenic *B. burgdorferi* organisms, together referred to as *B. burgdorferi sensu lato*, have been identified, and more groups surely exist. To date, North American strains have belonged to the first group, *B. burgdorferi sensu stricto*. Although all three of the identified groups have been found in Europe and Asia, most isolates there have been strains of group 2 (*B. garinii*) or group 3 (*B. afzelii*). These differences may well account for the clinical variations in the disease in different geographic regions.

### EPIDEMIOLOGY

The distribution of Lyme borreliosis correlates closely with the geographic ranges of ticks of the *Ixodes ricinus* complex: *I. scapularis* (also called *I. dammini*), *I. pacificus*, *I. ricinus*, and *I. persulcatus*. *I. scapularis* is the principal vector in the northeastern United States from Massachusetts to Maryland and in the midwestern states of Wisconsin and Minnesota. Surveys in these regions have documented infection in at least 20% of *I. scapularis* ticks; most cases of Lyme disease in the United States have occurred in these areas. *I. pacificus* is the vector in the western states of California and Oregon. The disease is acquired throughout Europe (from Great Britain to Scandinavia to European Russia), where *I. ricinus* is the vector, and in Asian Russia, China, and Japan, where *I. persulcatus* is the vector. These ticks transmit other diseases that may have similar symptoms. In the United States, *I. scapularis* also transmits babesiosis and ehrlichiosis; in Europe and Asia, *I. ricinus* and *I. persulcatus* also transmit tick-borne encephalitis.

Ticks of the *I. ricinus* complex feed once during each of the three stages of their usual

2-year life cycle. Typically, larval ticks take one blood meal in the late summer, nymphs (Fig. 176-CD1) feed during the following spring and early summer, and adults feed during autumn. For *I. scapularis* in the northeast, the white-footed mouse is the preferred host of the immature larval and nymphal ticks. It is critical that both of the tick's immature stages feed on the same host, because the life cycle of the spirochete depends on horizontal transmission: in early summer from infected nymphs to mice and in late summer from infected mice to larvae, which then molt to become the infected nymphs that will begin the cycle again the following year. It is the tiny nymphal tick that is primarily responsible for transmission of the disease to humans during the early summer months. White-tailed deer, which are not involved in the life cycle of the spirochete, are the preferred host for the adult stage of *I. scapularis* and seem to be critical to the tick's survival. The adult tick occasionally transmits the spirochete to humans during the fall, but at this stage the tick is considerably larger and easier to recognize.

Lyme disease is now the most common vector-borne infection in the United States. Since surveillance was begun in 1982, more than 100,000 cases have been reported to the Centers for Disease Control and Prevention (CDC); during the 1990s, more than 10,000 new cases have been reported each summer. Cases have been noted in 48 states, but the life cycle of *B. burgdorferi* has been identified in only 19 states. Cases have occurred in association with hiking, camping, or hunting trips and with residence in wooded or rural areas. Persons of all ages and both sexes are affected.

## PATHOGENESIS

To maintain its complex enzootic cycle, *B. burgdorferi* must adapt to two markedly different environments: the tick and the mammalian host. The spirochete expresses outer-surface proteins A and B (OspA and OspB) in the midgut of the tick, whereas OspC is upregulated as the organism travels to the tick's salivary gland and thence to the mammalian host.

After injection into the human skin, *B. burgdorferi* may migrate outward, producingEM, and may spread hematogenously to other organs. Spread within the human host is probably facilitated through binding to the spirochete's surface by human plasminogen and urokinase-type plasminogen activator, which activates plasmin, a potent protease. The spirochete can adhere to many types of mammalian cells; it binds specifically to certain ubiquitous host integrin receptors in the extracellular matrix, to vitronectin and fibronectin, and to matrix glycosaminoglycans. *B. burgdorferi* seems to have a particular tropism for tissues of the skin, nervous system, atrioventricular node, and joints, from all of which it has been cultured, seen in histologic sections, or (more commonly) detected (via its DNA) by the polymerase chain reaction (PCR). These findings and the response of all stages of the disease to antibiotic therapy suggest that the organism persists in affected tissues throughout the illness, but the mechanisms of persistent infection are not yet clear.

The immune response in Lyme disease develops gradually. After the first several weeks of infection, mononuclear cells generally exhibit heightened responsiveness to *B. burgdorferi* antigens, and evidence of B cell hyperactivity is found, including elevated total serum IgM levels, cryoprecipitates, and circulating immune complexes. Titers of

specific IgM antibody to *B. burgdorferi* peak between the third and sixth week after disease onset. The specific IgG response develops gradually over months, with response to an increasing array of 12 or more spirochetal polypeptides and maximal expansion during the period of arthritis. The spirochete is a potent inducer of proinflammatory cytokines, including tumor necrosis factor a and interleukin 1b. Histologic examination of all affected tissues reveals an infiltration of lymphocytes and plasma cells with some degree of vascular damage (including mild vasculitis or hypervascular occlusion), suggesting that the spirochete may have been present in or around blood vessels.

## CLINICAL MANIFESTATIONS

**Early Infection: Stage 1 (Localized Infection)** After an incubation period of 3 to 32 days,EM, which occurs at the site of the tick bite, usually begins as a red macule or papule that expands slowly to form a large annular lesion, most often with a bright red outer border and partial central clearing (Plate IID-46,Fig. 176-CD2). Because of the small size of ixodid ticks, most patients do not remember the preceding tick bite. The center of the lesion sometimes becomes intensely erythematous and indurated, vesicular, or necrotic. In other instances, the expanding lesion remains an even, intense red; several red rings are found within an outside ring; or the central area turns blue before the lesion clears. Although EM can be located anywhere, the thigh, groin, and axilla are particularly common sites. The lesion is warm but not often painful. Perhaps as many as 25% of patients do not exhibit this characteristic skin manifestation.

**Early Infection: Stage 2 (Disseminated Infection)** Within days or weeks after the onset ofEM, the organism often spreads hematogenously to many sites. In these cases patients frequently develop secondary annular skin lesions similar in appearance to the initial lesion. Skin involvement is commonly accompanied by severe headache, mild stiffness of the neck, fever, chills, migratory musculoskeletal pain, arthralgias, and profound malaise and fatigue. Less common manifestations include generalized lymphadenopathy or splenomegaly, hepatitis, sore throat, nonproductive cough, conjunctivitis, iritis, or testicular swelling. Except for fatigue and lethargy, which are often constant, the early signs and symptoms of Lyme disease are typically intermittent and changing. Even in untreated patients, the early symptoms usually become less severe or disappear within several weeks.

Symptoms suggestive of meningeal irritation may develop early in Lyme disease whenEM is present but usually are not associated with cerebrospinal fluid (CSF) pleocytosis or an objective neurologic deficit. After several weeks or months, about 15% of untreated patients develop frank neurologic abnormalities, including meningitis, subtle encephalitic signs, cranial neuritis (including bilateral facial palsy), motor or sensory radiculoneuropathy, mononeuritis multiplex, or myelitis -- alone or in various combinations. In the United States, the usual pattern consists of fluctuating symptoms of meningitis accompanied by facial palsy and peripheral radiculoneuropathy. Lymphocytic pleocytosis (about 100 cells per microliter) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations. In Europe and Asia, the first neurologic sign is characteristically radicular pain, which is followed by the development of CSF pleocytosis (called *Bannwarth's syndrome*), but meningeal or encephalitic signs are frequently absent. These early neurologic abnormalities usually

resolve completely within months, but chronic neurologic disease may occur later.

Within several weeks after the onset of illness, about 8% of patients develop cardiac involvement. The most common abnormality is a fluctuating degree of atrioventricular block (first-degree, Wenckebach, or complete heart block). Some patients have more diffuse cardiac involvement, including electrocardiographic changes indicative of acute myopericarditis, left ventricular dysfunction evident on radionuclide scans, or (in rare cases) cardiomegaly or pancarditis. Cardiac involvement usually lasts for only a few weeks but may recur. Chronic cardiomyopathy caused by *B. burgdorferi* has been reported in Europe.

During this stage, musculoskeletal pain is common. The typical pattern consists of migratory pain in joints, tendons, bursae, muscles, or bones (usually without joint swelling) lasting for hours or days and affecting one or two locations at a time.

**Late Infection: Stage 3 (Persistent Infection)** Months after the onset of infection, about 60% of patients in the United States who have received no antibiotic treatment develop frank arthritis. The typical pattern comprises intermittent attacks of oligoarticular arthritis in large joints (especially the knees), lasting for weeks to months in a given joint. Small joints and periarticular sites also may be affected, primarily during early attacks. The number of patients who continue to have recurrent attacks decreases each year. However, in a small percentage of cases, involvement of large joints -- usually one or both knees -- becomes chronic and may lead to erosion of cartilage and bone. These patients have a higher frequency of the class II major histocompatibility complex alleles associated with rheumatoid arthritis, particularly HLA-DRBI*0401 or *0101 alleles, than patients with brief Lyme arthritis or normal control subjects. Moreover, they may have persistent arthritis for months or even several years after the apparent eradication of spirochetes from the joints with antibiotic therapy. In these genetically susceptible individuals, autoimmunity may develop within the proinflammatory milieu of the joints because of molecular mimicry between the dominant T cell epitope of OspA and human lymphocyte function-associated antigen 1 (hLFA-1).

White cell counts in joint fluid range from 500 to 110,000/uL (average, 25,000/uL); most of these cells are polymorphonuclear leukocytes. Tests for rheumatoid factor or antinuclear antibodies usually give negative results. Examination of synovial biopsy samples reveals fibrin deposits, villous hypertrophy, vascular proliferation, microangiopathic lesions, and a heavy infiltration of lymphocytes and plasma cells.

Although less common, chronic neurologic involvement may also become apparent months or years after the onset of infection, sometimes following long periods of latent infection. The most common form of chronic central nervous system involvement is subtle encephalopathy affecting memory, mood, or sleep and often accompanied by axonal polyneuropathy manifested as either distal paresthesia or spinal radicular pain. Patients with encephalopathy frequently have evidence of memory impairment in neuropsychological tests and abnormal results inCSFanalyses. In cases with polyneuropathy, electromyography generally shows extensive abnormalities of proximal and distal nerve segments. Encephalomyelitis or leukoencephalitis, a rare manifestation of Lyme borreliosis reported primarily in Europe, is a severe neurologic disorder that may include spastic paraparesis, upper motor-neuron bladder dysfunction, and lesions

in the periventricular white matter. The prolonged course of chronic neuroborreliosis following periods of latent infection is reminiscent of tertiary neurosyphilis.

Acrodermatitis chronica atrophicans (Fig. 176-CD3), the late skin manifestation of the disorder, has been associated primarily with *B. afzelii* infection in Europe and Asia. It has been observed primarily in elderly women. The skin lesions, which are usually found on the acral surface of an arm or leg, begin insidiously with reddish-violaceous discoloration; they become sclerotic or atrophic over a period of years.

**DIAGNOSIS**

Lyme disease is usually diagnosed by the recognition of a characteristic clinical picture with serologic confirmation. Although serologic testing may yield negative results during the first several weeks of infection, most patients have a positive antibody response to *B. burgdorferi* after that time. The limitation of serologic tests is that they do not clearly distinguish between active and inactive infection. Patients with previous Lyme disease -- particularly in cases progressing to late stages -- often remain seropositive for years, even after adequate antibiotic treatment. In addition, some patients are seropositive because of asymptomatic infection. If these individuals subsequently develop another illness, the positive serologic test for Lyme disease may cause diagnostic confusion. On the other hand, a few patients who receive inadequate antibiotic therapy during the first several weeks of infection develop subtle joint or neurologic symptoms but are seronegative. The important point is that seronegative Lyme disease is usually a mild, attenuated illness.

For serologic analysis in Lyme disease, theCDCrecommends a two-step approach in which samples are first tested by enzyme-linked immunosorbent assay (ELISA) and equivocal or positive results are then tested by western blotting. During the first month of infection, both IgM and IgG responses to the spirochete should be determined, preferably in both acute- and convalescent-phase serum samples. Approximately 20 to 30% of patients have a positive response detectable in acute-phase samples, whereas about 70 to 80% have a positive response during convalescence (2 to 4 weeks later). After that time, the great majority of patients continue to have a positive IgG antibody response, and a single test (that for IgG) is usually sufficient. In persons with illness of longer than 1 month's duration, a positive IgM test result alone is likely to be false-positive; therefore, a positive IgM test should not be used to support the diagnosis in such patients. According to current criteria adopted by the CDC, an IgM western blot is considered positive if two of the following three bands are present: 23, 39, and 41 kDa. However, the combination of the 23- and 41-kDa bands may still represent a false-positive result. An IgG blot is considered positive if 5 of the following 10 bands are present: 18, 23, 28, 30, 39, 41, 45, 58, 66, and 93 kDa.

Because serologic tests do not distinguish between active and inactive infection, tests that detect the spirochete directly are being researched. *B. burgdorferi* may be cultured from skin lesions of patients with the disorder, but its culture from other sites has been a low-yield proposition. Detection of spirochetal DNA byPCR may serve as a substitute for culture in cases of Lyme arthritis. In one study, *B. burgdorferi* DNA was detected in synovial fluid samples from 75 (85%) of 88 patients and in none of 64 control samples. However, the sensitivity of PCR determinations inCSF from patients with

neuroborreliosis has been much lower. There seems to be little if any role for PCR in the detection of *B. burgdorferi* DNA in blood or urine samples.

## DIFFERENTIAL DIAGNOSIS

ClassicEM is a slowly expanding erythema with partial central clearing. If the lesion expands little, it may represent the red papule of an uninfected tick bite. If the lesion expands rapidly, it may represent cellulitis (e.g., streptococcal cellulitis) or an allergic reaction, perhaps to tick saliva. Patients with secondary annular lesions may be thought to have erythema multiforme, but neither the development of blistering mucosal lesions nor the involvement of the palms or soles is a feature of *B. burgdorferi* infection. In the southeastern United States, an EM-like skin lesion, sometimes with mild systemic symptoms, may be associated with *Amblyomma americanum* tick bites, but the cause of this illness has not yet been identified.

Later in the infection, the most common problem in diagnosis is to mistake Lyme disease for chronic fatigue syndrome or fibromyalgia. This difficulty is compounded by the fact that a small percentage of patients do in fact develop these chronic pain or fatigue syndromes in association with or soon after Lyme disease. Compared with Lyme disease, chronic fatigue syndrome (Chap. 384) or fibromyalgia tends to produce more generalized and disabling symptoms, including marked fatigue, severe headache, diffuse musculoskeletal pain, multiple symmetric tender points in characteristic locations, pain and stiffness in many joints, diffuse dysesthesia, difficulty with concentration, and sleep disturbances. Patients with chronic fatigue syndrome or fibromyalgia lack evidence of joint inflammation; they have normal results in neurologic tests; and they usually have a greater degree of anxiety and depression than patients with chronic neuroborreliosis.

## TREATMENT

As outlined in the algorithm in Fig. 176-1, the various manifestations of Lyme disease can usually be treated successfully with orally administered antibiotics; the exceptions are objective neurologic abnormalities and third-degree atrioventricular heart block, which seem to require intravenous therapy. For early Lyme disease, doxycycline is effective in men and in nonpregnant women. An advantage of this regimen is that it is also effective against the agent of human granulocytic ehrlichiosis, which is transmitted by the same tick that transmits the Lyme disease agent. Amoxicillin, cefuroxime axetil, and erythromycin or its congeners are second-, third-, and fourth-choice alternatives, respectively. In children, amoxicillin is effective (not more than 2 g/d); in cases of penicillin allergy, cefuroxime axetil or erythromycin may be used. For patients with infection localized to the skin, a 20-day course of therapy is generally sufficient; in contrast, for patients with disseminated infection, a 30-day course is recommended. Approximately 15% of patients experience a Jarisch-Herxheimer-like reaction during the first 24 h of therapy.

These oral antibiotic regimens, when given for 30 to 60 days, are effective for the treatment of Lyme arthritis. However, the response to oral therapy may be slower than that to intravenous therapy. In the small percentage of patients with arthritis in whom arthritic symptoms persist for months or even years after the apparent eradication of

spirochetes from the joints with antimicrobial therapy, treatment with anti-inflammatory agents or synovectomy may be successful.

For objective neurologic abnormalities (with the possible exception of facial palsy alone), parenteral antibiotic therapy seems to be necessary. Intravenous ceftriaxone, given for 4 weeks, is most commonly used for this purpose, but intravenous cefotaxime or intravenous penicillin G for the same duration may also be effective. In patients with high-degree atrioventricular block or a PR interval of greater than 0.3 s, intravenous therapy for at least part of the course and cardiac monitoring are recommended. Prior to the use of antibiotics for the treatment of Lyme disease, the degree of heart block was found to decrease rapidly with prednisone (40 to 60 mg/d). Although rarely used today, glucocorticoids may be of benefit in patients with complete heart block or congestive heart failure if antimicrobial therapy alone does not result in improvement within 24 h.

It is unclear how and whether asymptomatic infection should be treated, but patients with such infection are often given a course of oral antibiotics. The appropriate treatment for Lyme disease during pregnancy is also unclear. Because the risk of maternal-fetal transmission seems to be very low, standard therapy for the documented stage and manifestation of the illness may be sufficient. Relapse may follow the use of any of the antibiotic regimens for Lyme disease, and a second course of therapy may be necessary. On the other hand, in patients who develop chronic fatigue syndrome or fibromyalgia after Lyme disease, further antibiotic therapy does not seem to be of benefit.

The risk of infection with *B. burgdorferi* after a recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if the tick is engorged, if follow-up is difficult, or if the patient is quite anxious, therapy with amoxicillin or doxycycline for 10 days is likely to prevent Lyme disease.

## PROGNOSIS

The response to treatment is best early in the disease. Later treatment of Lyme borreliosis is still effective, but convalescence may be longer. Eventually, most patients recover with minimal or no residual deficits.

## ALGORITHM FOR TESTING AND THERAPY

According to guidelines recently published by the American College of Physicians, empirical antibiotic therapy without serologic testing is recommended for patients with a high pretest probability of Lyme disease (such as those withEM); two-step testing (byELISAand, if positive, by western blot) is recommended for patients with an intermediate pretest probability (such as those with recurrent oligoarticular arthritis); and neither testing nor treatment is recommended for patients with a low pretest probability (such as those with nonspecific symptoms of myalgias, arthralgias, or fatigue).

## REINFECTION

Reinfection may occur afterEM when patients are treated with antimicrobial agents. In such cases, the immune response is not adequate to provide protection from

subsequent infection. However, patients who develop an expanded immune response to the spirochete over a period of months (such as those with Lyme arthritis) have protective immunity for a period of years and do not acquire the infection again.

## VACCINATION

A vaccine is now available for the prevention of Lyme disease in the United States. It consists of a recombinant outer-surface lipoprotein A (L-OspA) with adjuvant. High-titered antibody to OspA is necessary for protection. In a phase 3 efficacy trial in which subjects were given three doses of vaccine or placebo on a 0-, 1-, and 12-month schedule, vaccine efficacy in preventing definite cases of Lyme disease was 49% during the first year (after two doses) and 76% in year 2 (after three doses). Equivalent antibody titers may be obtained if the three doses are given on a 0-, 1-, and 2-month schedule. The third dose should be given in April so that the vaccine recipient will have peak antibody titers during the summer tick-transmission season. Although long-term data are not yet available, yearly booster injections may be necessary. Vaccine injection may cause a mild to moderate local or systemic reaction usually lasting for only a few days. Vaccination should be considered for individuals who live in areas that are highly endemic for the infection and who have frequent exposure to tick habitats.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 10 -*RICKETTSIA, MYCOPLASMA,* AND *CHLAMYDIA*

## 177. RICKETTSIAL DISEASES - *David Walker*, *Didier Raoult*, *J. Stephen Dumler*, *Thomas Marrie*

The rickettsiae make up a family of gram-negative coccobacilli and short bacilli that grow strictly in eukaryotic cells. Characteristics of these organisms include their obligately intracellular location and persistence. The pathogenic rickettsiae move through mammalian reservoirs; they are transmitted by insect or tick vectors. Except for louse-borne typhus, humans are incidental hosts. Among rickettsiae, *Coxiella burnetii* (the agent of Q fever) is notorious for its ability to survive for an extended period outside of the reservoir or vector and for its extreme infectiousness: inhalation of a single microorganism can cause pneumonia. Clinical infections with rickettsiae can be classified into five general groups: (1) tick- and gamasid mite-borne, spotted fever group (SFG) rickettsial diseases; (2) flea- and louse-borne typhus group rickettsial diseases; (3) chigger-borne scrub typhus; (4) ehrlichioses; and (5) Q fever. The rickettsiae that cause spotted fevers, typhus, and scrub typhus are listed along with their vectors, geographic ranges, and associated diseases inTable 177-1.

### TICK- AND MITE-BORNE SPOTTED FEVERS

### ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever (RMSF), the most severe of the rickettsial diseases, is caused by *Rickettsia rickettsii*. This organism possesses two major immunodominant surface-exposed proteins, rOmpA and rOmpB, which have species-specific conformational epitopes. rOmpA functions as an adhesin for the host cell; rOmpB, the most abundant outer-membrane protein, shares genetic sequences and limited antigens with typhus group rickettsiae. This small (0.3 um by 1.0 um) bacillus has a gram-negative cell wall structure; its lipopolysaccharide shares antigens mainly within theSFG and is not endotoxic in the quantities found in human infections.

Discovered in the American West in the late nineteenth century,RMSF is at present documented in 48 states, Canada, Mexico, Costa Rica, Panama, Colombia, and Brazil. It is transmitted by *Dermacentor variabilis*, the American dog tick, in the eastern two-thirds of the United States and California; by *D. andersoni*, the Rocky Mountain wood tick, in the western United States; by *Rhipicephalus sanguineus* in Mexico; and by *Amblyomma cajennense* in Central and South America. Maintained principally by transovarian transmission from one generation of ticks to the next, *R. rickettsii* can be acquired by uninfected ticks through the ingestion of a blood meal from rickettsemic small mammals.

Humans become infected during the active season of the vector tick species. In northern areas, cases occur mainly in the spring; in warmer southern states, most cases occur from May to September, although some cases are reported in the winter. Although 4% of *D. variabilis* ticks contain rickettsiae, the vast majority of these are nonpathogenic species such as *R. montana* and *R. bellii*. The likelihood of an individual tick's containing *R. rickettsii* is remote. From 1988 to 1997, the reported incidence ofRMSF has been in the range of 0.16 to 0.26 cases per 100,000 population in the

United States. This rate is probably an underestimate, since the diagnosis is difficult and reporting incomplete. The 5- to 9-year-old age group has the highest incidence. The mortality rate was 20 to 25% in the preantibiotic era and now remains at about 5% because of delayed diagnosis and treatment. The case-fatality ratio is higher for males than females and increases with each decade of life above age 20.

**Pathogenesis** *R. rickettsii* organisms are inoculated into the dermis along with secretions of the tick's salivary glands after ³6 h of feeding. Rickettsiae spread lymphohematogenously throughout the body, attach via rOmpA to the endothelial cell membrane, and induce their own engulfment. Once intracellularly located, they escape rapidly from the phagosome, replicate in the cytosol by binary fission, and spread from cell to cell, propelled by polar polymerization of the host cell's actin. The result is numerous foci of contiguous infected endothelial cells that are extensive enough to manifest clinically after a dose-dependent incubation period of approximately 1 week (range, 2 to 14 days). *R. rickettsii* is more invasive than other rickettsiae, routinely spreading to infect vascular smooth-muscle cells. Despite frequent statements to the contrary, occlusive thrombosis and ischemic necrosis are not the fundamental pathologic basis for tissue and organ injury inRMSF. Instead, increased vascular permeability, with resulting edema, hypovolemia, and ischemia, is responsible. Indeed, immunohistologic studies of severely infected humans and animals have demonstrated numerous zones of infected endothelium, only a small proportion of which contain thrombi. The thrombi are usually located to one side of the lumen, which is not occluded. These hemostatic plugs appear to be an appropriate host response rather than a pathogenic process. Consumption of platelets results in thrombocytopenia in 32 to 52% of patients, but disseminated intravascular coagulation with hypofibrinogenemia is rare. Activation of platelets, generation of thrombin, and activation of the fibrinolytic system all appear to be homeostatic physiologic responses to endothelial injury.

**Clinical Manifestations** Early in the illness, when medical attention usually is first sought,RMSF is difficult to distinguish from many self-limiting viral illnesses. Fever, headache, malaise, myalgia, nausea, vomiting, and anorexia are the most frequent symptoms during the first 3 days. The patient becomes progressively more ill as vascular infection and injury advance. In one large series, only one-third of patients were diagnosed with presumptive RMSF early in the clinical course and treated appropriately as outpatients. In the tertiary care setting, RMSF is all too often recognized only when its late severe manifestations, developing at the end of the first week or in the second week of illness in patients without appropriate treatment, prompt admission to the intensive care unit.

The progressive nature of the infection is clearly manifested in the skin. Rash is evident in only 14% of patients on the first day of illness and in only 49% during the first 3 days. Macules (1 to 5 mm) appear first on the wrists and ankles (Figs. 177-CD1,177-CD2) and then on the remainder of the extremities and the trunk. Later, more severe vascular damage results in frank hemorrhage at the center of the maculopapule (Fig. 177-CD3), a petechia that does not disappear upon compression (Plate IID-45). This sequence of events is sometimes delayed or aborted by effective treatment. In fact, rash appears on day 6 or later in 20% of cases and does not appear at all in 9 to 16% of cases, including some with severe visceral lesions that result in death. Petechiae occur in 41 to 59% of cases, appearing on or after day 6 in 74% of cases that include a rash. Involvement of

the palms and soles, often considered diagnostically important, usually occurs relatively late in the course (after day 5 in 43% of cases) and does not occur at all in 18 to 64% of cases.

The microcirculation, both systemic and pulmonary, is the target of intracellular rickettsial infection, and the clinical manifestations reflect the ensuing vascular changes. Widespread increased vascular permeability results in edema, decreased plasma volume, hypoalbuminemia, reduced serum oncotic pressure, and prerenal azotemia. Hypotension occurs in 17% of cases. Extensive infection of the pulmonary microcirculation is associated with noncardiogenic pulmonary edema. Cardiac involvement is most frequently manifested as dysrhythmia, which is detected in 7 to 16% of cases. Pulmonary involvement, often a major factor in fatal cases, is observed in 17% of cases, of which 12% are considered to represent severe respiratory disease and 8% require mechanical ventilation.

Central nervous system (CNS) involvement is the other important determinant of the outcome ofRMSF. Encephalitis, presenting as confusion or lethargy, is apparent in 26 to 28% of cases. Progressively severe encephalitis manifests as stupor or delirium in 21 to 26% of cases, as ataxia in 18%, as coma in 9 to 10%, and as seizures in 8%. Cranial nerve palsy, hearing loss, severe vertigo, nystagmus, dysarthria, aphasia, unilateral corticospinal signs, ankle clonus, extensor toe signs, hyperreflexia, spasticity, fasciculations, athetosis, neurogenic bladder, hemiplegia, paraplegia, and complete paralysis have been reported. Meningoencephalitis results in cerebrospinal fluid (CSF) pleocytosis in 34 to 38% of cases; usually there are 10 to 100 cells per microliter with a mononuclear predominance, but occasionally there are more than 100 cells per microliter and a polymorphonuclear predominance. The CSF protein concentration is increased in 30 to 35% of cases, but the CSF glucose concentration is usually normal.

Renal failure, which occurs in more severely ill patients, is often reversible with rehydration. However, in the most severe cases, shock results in acute tubular necrosis-induced renal failure, which often requires hemodialysis.

Hepatic injury is manifested in 38% of cases as mildly or moderately increased serum aminotransferase concentrations and is due to focal death of individual hepatocytes, but hepatic failure does not occur. Jaundice is recognized in 8 to 9% of cases and an elevated serum bilirubin concentration in 18 to 30%. Marked hyperbilirubinemia occasionally occurs, probably as a consequence of both hemolysis and hepatocytic injury.

Bleeding is a potentially life-threatening effect of severe vascular damage. Anemia develops in 30% of cases and is severe enough to require red blood cell transfusions in 11%. Blood is detected in the stools or vomitus of 10% of patients, and death has followed massive upper gastrointestinal hemorrhage.

Other characteristic clinical laboratory findings include a normal white blood cell count with increased numbers of immature myeloid cells, increased plasma levels of proteins of the acute-phase response (C-reactive protein, fibrinogen, ferritin, and others), and hyponatremia (in 56% of cases) due to the appropriate secretion of antidiuretic hormone in response to the hypovolemic state. Skeletal muscle injury, clinically manifested as

myositis, has been documented in several individual cases by the detection of marked elevations in serum creatine kinase or of histopathologic evidence of vascular injury in skeletal muscle and multifocal rhabdomyonecrosis. Ocular involvement includes conjunctivitis in 30% of cases and retinal vein engorgement, flame hemorrhages, arterial occlusion, and papilledema with normalCSFpressure in some instances.

In untreated cases, death usually occurs 8 to 15 days after the onset of illness. A rare presentation, fulminantRMSF, is fatal within 5 days after onset. This fulminant presentation has been associated with RMSF in black males who have glucose-6-phosphate dehydrogenase (G6PD) deficiency and is thought to be related to an undefined effect of hemolysis on the rickettsial infection. Although survivors of RMSF usually appear to return to their previous state of health, permanent sequelae, including neurologic deficits and amputation of gangrenous extremities, may follow severe illness.

**Diagnosis** The diagnosis ofRMSFduring the acute stage is more difficult than is generally appreciated. Clinical and epidemiologic considerations are more important than laboratory features early in the illness. The most important epidemiologic factor is a history of exposure within the 12 days preceding disease onset to a potentially tick-infested environment during a season of possible tick activity. However, only 60% of patients actually recall being bitten by a tick during the incubation period.

The differential diagnosis for early clinical manifestations ofRMSF(fever, headache, and myalgia without a rash) includes influenza, enteroviral infection, infectious mononucleosis, viral hepatitis, leptospirosis, typhoid fever, gram-negative or -positive bacterial sepsis, human monocytic or granulocytic ehrlichiosis, murine typhus, sylvatic flying-squirrel typhus, and rickettsialpox. Enterocolitis may be suggested by nausea, vomiting, and abdominal pain; prominence of abdominal tenderness has resulted in exploratory laparotomy.CNSinvolvement may masquerade as bacterial and viral meningoencephalitis, with seizures, coma, neurologic signs, andCSFabnormalities. Cough, pulmonary signs, and chest roentgenographic opacities may lead to a diagnostic consideration of bronchitis or pneumonia.

During the first 3 days of illness, only 3% of patients exhibit the classic triad of fever, rash, and history of tick exposure. When a rash appears, a diagnosis ofRMSFshould certainly be considered. However, many illnesses considered in the differential diagnosis may also be associated with a rash, including rubeola, rubella, meningococcemia, disseminated gonococcal infection, secondary syphilis, toxic shock syndrome, drug hypersensitivity, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Kawasaki syndrome, and immune complex vasculitis. The converse is also true: any person in an endemic area with a provisional diagnosis of one of the above illnesses may have RMSF.

The most common serologic test for confirmation of the diagnosis is the indirect immunofluorescence assay. Between 7 and 10 days after onset, a diagnostic titer of$^{3}$1:64 is usually detectable. Latex agglutination and a solid-state enzyme immunoassay are also available commercially. Latex agglutination usually yields a diagnostic titer of$^{3}$1:128 at 7 to 9 days after onset. The sensitivity and specificity of the indirect immunofluorescence assay are 94 to 100% and 100%, respectively, and the latex agglutination test has a sensitivity of 71 to 94% and a specificity of 96 to 99%. The

performance of the solid-state immunoassay has not been reported. It is important to understand that serologic tests forRMSF are usually negative at the time of presentation for medical care and that treatment should not be delayed while a positive serologic result is awaited.

The only diagnostic test that is useful during the acute illness is immunohistologic examination (immunofluorescence or immunoenzyme staining) of a cutaneous biopsy of a rash lesion for *R. rickettsii*. Examination of a 3-mm punch biopsy of such a lesion is 70% sensitive and 100% specific. Polymerase chain reaction (PCR) amplification and detection of *R. rickettsii* DNA in peripheral blood is an insensitive approach except in the preterminal state; rickettsiae are present in large quantities in heavily infected foci of endothelial cells but in relatively low quantities in the circulation. Cultivation of rickettsiae in cell culture is technically feasible but is seldom undertaken because of biohazard and technologic concerns.

## TREATMENT

The drug of choice for the treatment of both children and adults withRMSF is doxycycline, except when the patient is pregnant or allergic to the drug. Doxycycline is administered orally (or, in the presence of coma or vomiting, intravenously) at 200 mg/d in two divided doses. For children with RMSF reinfection, up to five courses of doxycycline may be administered with minimal risk of dental staining. Other regimens include oral tetracycline (25 to 50 mg/kg per day) in four divided doses. b-Lactam antibiotics, erythromycin, and aminoglycosides have no role in the treatment of RMSF, and sulfa-containing drugs are likely to exacerbate this infection. There is not enough clinical experience to comment on the use of fluoroquinolones in this setting. The most seriously ill patients are managed in intensive care units, with careful administration of fluids to achieve optimal tissue perfusion without precipitating noncardiogenic pulmonary edema. In some severely ill patients, hypoxemia requires intubation and mechanical ventilation; oliguric or anuric acute renal failure requires hemodialysis; seizures necessitate the use of antiseizure medication; anemia or severe hemorrhage necessitates transfusions of packed red blood cells; and bleeding with severe thrombocytopenia requires platelet transfusions. Heparin is not a useful component of treatment, and there is no evidence that glucocorticoids, although frequently administered, affect outcome.

**Prevention** Avoidance of tick bites is the only available preventive approach. Protective clothing and tick repellents, which could reduce the risk, are seldom actually used. After possible tick exposure, it is wise to inspect the body once or twice a day and remove ticks before they can inoculate rickettsiae.

## MEDITERRANEAN SPOTTED FEVER (BOUTONNEUSE FEVER) AND OTHER SPOTTED FEVERS

The etiologic agent of Mediterranean spotted fever, *R. conorii*, is prevalent in southern Europe (below the 45th parallel), all of Africa, and southwestern and south-central Asia. The tick vector and reservoir is *R. sanguineus*, the dog brown tick. The name of this disease varies with the region in which it occurs; examples include Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan spotted fever. Whatever the

designation, the disease is characterized by a high fever, rash, and -- in most geographic locales -- an inoculation eschar (*tache noire*) at the site of the tick bite. A severe form of the disease, associated with a 50% mortality rate, has been observed in patients with diabetes, alcoholism, or heart failure.

*African tick-bite fever*, which is caused by *R. africae* and has been recognized since the beginning of the twentieth century, was first documented in the modern era in Zimbabwe in 1992. The disease occurs in rural areas and follows bites by ticks of cattle and wild animals. *R. africae* is prevalent in *Amblyomma hebraeum* and *A. variegatum* ticks, which readily feed on humans. Cases have been confirmed not only in Zimbabwe but also in Tanzania and South Africa, and the disease is prevalent in the Caribbean islands of Guadeloupe. The incubation period is 7 days. The illness is mild and consists of headache, fever, eschar at the tick bite site, and regional lymphadenopathy. *Amblyomma* ticks often feed in groups, and several ticks may be found on one patient, with the subsequent development of multiple eschars. Rash is frequently lacking or transient and may be vesicular. African tick-bite fever is the most prevalent rickettsiosis worldwide, and, as tourism to sub-Saharan Africa increases, it is expected that more cases will be seen in non-African countries.

*Rickettsia japonica* causes *Japanese spotted fever* or *Oriental spotted fever*. Patients present with fever, cutaneous eruption, and an inoculation eschar. In Australia, two spotted fevers have been described. *Queensland tick typhus* is due to *R. australis* and is transmitted by *Ixodes holocyclus*. The skin rash in this disease is usually maculopapular but is sometimes vesicular, and there is an inoculation eschar. *Flinders Island spotted fever*, observed on an island close to Tasmania, is due to *R. honei*. In France, a case of *atypical Lyme disease* caused by *R. slovaca* and two cases of infection with *R. mongolotimonae* have been reported.

**Diagnosis** The diagnosis of these tick-borne spotted fevers is based on clinical and epidemiologic findings and is confirmed by cell-culture isolation of rickettsiae, byPCR of skin biopsies (a method not available in most laboratories), or by serology. The identification of specific species requires cross-adsorption (Table 177-2). In an endemic area, patients presenting with fever, rash, and/or a skin lesion consisting of a black necrotic area or a crust surrounded by erythema should be considered to have one of these rickettsial spotted fevers.

## TREATMENT

SeeTable 177-2.

## RICKETTSIALPOX

Rickettsialpox was first described in 1946 by a general practitioner in New York City and soon afterwards was shown to be caused by a distinct species, *R. akari*. This organism was isolated from mice and their mites (*Liponyssoides sanguineus*), which maintain the organisms by transovarian transmission. *R. akari* shares lipopolysaccharide antigens with other members of theSFG.

**Epidemiology** More than 100 cases of rickettsialpox were diagnosed annually in the

northeastern United States in the late 1940s and the 1950s, and outbreaks occurred in the Ukraine in the 1950s. However, few cases are diagnosed currently. Recently, a culture-confirmed case of rickettsialpox was documented in southern Europe. This case was initially misdiagnosed as Mediterranean spotted fever on the basis of the development of serum antibodies cross-reactive with *R. conorii*. Cases have also been reported in Arizona, Utah, and Ohio.

**Clinical Manifestations** A papule forms at the site of the mite bite. This lesion develops a central vesicle that becomes a 1- to 2.5-cm painless black crusted eschar surrounded by an erythematous halo (Fig. 177-CD4). Enlargement of the lymph nodes draining the region of the eschar suggests initial lymphogenous spread. After a 10-day incubation period, during which the eschar and regional lymphadenopathy frequently go unnoticed, the onset of illness is marked by malaise, chills, fever, headache, and myalgia. A macular rash appears 2 to 6 days after onset and evolves sequentially into papules, vesicles, and crusts that heal without scarring. In some cases the rash remains macular or maculopapular. Some patients suffer nausea, vomiting, abdominal pain, cough, conjunctivitis, or photophobia. Untreated rickettsialpox is not fatal, with fever lasting 6 to 10 days.

**Diagnosis and Treatment** SeeTable 177-2.

## FLEA- AND LOUSE-BORNE RICKETTSIAL DISEASES

### ENDEMIC MURINE TYPHUS (FLEA-BORNE)

Murine typhus was postulated to be a distinct disease, with rats as the reservoir and fleas as the vector, by Maxcy in 1926. Dyer isolated the etiologic agent, *R. typhi*, from rats and fleas in 1931. By the end of World War II, murine typhus was known to be a global disease. A novel typhus group *Rickettsia* has now been shown to be maintained vertically in cat fleas and to cause human infection. This flea-transmitted species, *R. felis*, reportedly contains antigens most closely resembling typhus group rickettsiae but genetically is anSFGorganism. *R. felis* has been found in 4% of cat fleas and in 33% of opossums collected in the vicinity of human murine typhus-like cases in southern Texas.

**Epidemiology** *R. typhi* is maintained in mammalian host/flea cycles, with rats (*Rattus rattus* and *R. norvegicus*) and the Oriental rat flea (*Xenopsylla cheopis*) as the classic zoonotic niche. Fleas acquire *R. typhi* from rickettsemic rats and carry the organism throughout the rest of their lifespan. Nonimmune rats and humans are infected when rickettsia-laden flea feces are "scratched" into pruritic bite lesions; less frequently, the flea bite itself transmits the organisms. Yet another possible route of transmission is the inhalation of aerosolized flea feces. Infected rats appear healthy, although they are rickettsemic for approximately 2 weeks.

Currently, fewer than 100 cases of endemic typhus are reported annually in the United States. These cases occur mainly in southern Texas and southern California, where the classic rat-flea cycle is absent and an opossum-cat flea (*Ctenocephalides felis*) cycle is prominent. Although *X. cheopis* fleas are inefficient at the transovarian maintenance of *R. felis*, cat fleas are highly effective at vertical transmission of this organism, whose natural occurrence has been detected in fleas in California, Texas, and Oklahoma.

Infected opossums and cat fleas as well as a case of human infection were reported from Corpus Christi, Texas, in the same environment where humans, opossums, and cat fleas are infected with *R. typhi*. Cases of endemic typhus occur year-round, mainly in warm (often coastal) areas. This infection has also been reported from Greece, Spain, and Indonesia. The peak prevalence in southern Texas is from April through June and elsewhere is during the warm months of summer and early fall. Patients seldom recall a flea bite or exposure to fleas, although exposure to animals such as cats, opossums, raccoons, skunks, and rats is reported by nearly 40% of those who are questioned.

**Clinical Manifestations** The incubation period of experimental murine typhus in volunteers averages 11 days, with a range of 8 to 16 days. Close observation during this period reveals prodromal symptoms of headache, myalgia, arthralgia, nausea, and malaise developing 1 to 3 days before the abrupt onset of chills and fever. Nearly all patients experience nausea and vomiting early in the illness.

The duration of untreated illness averages 12 days, with a range of 9 to 18 days. Rash is present in only 13% of patients at the time of presentation for medical care (usually about 4 days after onset of symptoms), appearing an average of 2 days later in half of the remaining patients and never appearing in the other half. The initial macular rash is often detected by careful inspection of the axilla or the inner surface of the arm. Subsequently, the rash becomes maculopapular, involving the trunk more often than the extremities; it is seldom petechial and rarely involves the face, palms, or soles. A rash is detected in only 20% of patients with dark brown or black skin.

Pulmonary involvement is frequently prominent in murine typhus; 35% of patients have a hacking, nonproductive cough, and 23% of patients who undergo chest radiography have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions. Bibasilar rales are the most common pulmonary sign. Less common clinical symptoms and signs include abdominal pain, confusion, stupor, seizures, ataxia, coma, and jaundice. Clinical laboratory studies frequently reveal anemia and leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, mildly increased serum levels of hepatic aminotransferases, and prerenal azotemia. Complications may include respiratory failure requiring intubation and mechanical ventilation, hematemesis, cerebral hemorrhage, and hemolysis (in patients with G6PD deficiency and some hemoglobinopathies). The illness is severe enough to necessitate the admission of 10% of hospitalized patients to an intensive care unit. Greater severity is generally associated with old age, underlying disease, and treatment with a sulfa drug; the case-fatality rate is 1%. In a study of children with murine typhus, 50% suffered only nocturnal fevers, feeling well enough for active daytime play.

**Diagnosis and Treatment** See Table 177-2.

## EPIDEMIC TYPHUS (LOUSE-BORNE)

Epidemic typhus due to infection with *R. prowazekii* is transmitted by the human body louse (*Pediculus humanus corporis*), which lives on clothes and is found in poor hygienic conditions (especially in jails, where the disease it causes is called *jail fever*)

and usually in cold areas. Lice acquire *R. prowazekii* when they ingest a blood meal from a rickettsemic patient. The rickettsiae multiply in the midgut epithelial cells of the louse and spill over into the louse feces. The infected louse defecates during its blood meal, and the patient autoinoculates the organisms by scratching. The fact that the louse abandons dead hosts and patients with high fever (>40°C) improves its efficiency as a vector. Since the louse does not pass *R. prowazekii* to its offspring, the disease is usually spread from person to person by the louse-borne route. Lice die within 1 to 2 weeks after infection, turning red just prior to death -- hence the name *red louse disease*. This epidemic form of typhus is related to poverty, cold weather, war, and disasters and is currently prevalent in mountainous areas of Africa, South America, and Asia. A large outbreak involving 100,000 people in refugee camps in Burundi occurred in 1997, a small focus was reported in Russia for the first time in 1998, and sporadic cases have been reported from Algeria and from Peru. The global reemergence of the disease is due to proliferation of body lice. In the United States, sporadic cases of epidemic typhus are transmitted by flying-squirrel fleas. Eastern flying-squirrel (*Glaucomys volans*) lice and fleas have been found to be infected with *R. prowazekii*. The flying-squirrel fleas occasionally bite humans.

*Brill-Zinsser disease* is a recrudescent, mild form of epidemic typhus occurring years after the acute disease, probably as a result of immunosuppression or old age. Nathan Brill first identified recrudescent typhus in New York in 1898. In 1933 Hans Zinsser noted that more than 90% of patients with recrudescent typhus had emigrated from typhus-endemic areas of Europe. Strains of *R. prowazekii* indistinguishable from classic strains were isolated from patients with recrudescent typhus. Furthermore, *R. prowazekii* was isolated from the lymph nodes of patients undergoing elective surgery who had had typhus years earlier. Thus the typhus rickettsiae can remain dormant for years and can reactivate with waning immunity.

**Clinical Manifestations** After an incubation period of 1 week, the onset of illness is abrupt, with prostration, severe headache, and rapidly rising fever of 38.8 to 40.0°C (102 to 104°F). Cough is frequently prominent, occurring in 70% of patients. Myalgias are usually severe. In the outbreak in Burundi, the disease was referred to as *sutama* ("crouching"), the myalgias being so severe that patients crouched in an attempt to alleviate the pain. A rash begins on the upper trunk, usually on the fifth day, and then becomes generalized, involving all of the body except the face, palms, and soles. Initially, this rash is macular; without treatment, it becomes maculopapular, petechial, and confluent (Fig. 177-CD5). The rash is frequently absent or not detected on black skin in Africa, where 60% of patients have *spotless epidemic typhus*. Photophobia, with considerable conjunctival injection and eye pain, is frequent. The tongue may be dry, brown, and furred. Confusion and coma are common. Skin necrosis and gangrene of the digits as well as interstitial pneumonia have been noted in severe cases (Fig. 177-CD6). Untreated disease is fatal in 7 to 40% of cases, with outcome depending primarily on the condition of the host. Patients with untreated infections develop renal insufficiency and multiorgan involvement in which neurologic manifestations are frequently prominent. Overall, 12% of patients with epidemic typhus have neurologic involvement. North American *R. prowazekii* infection transmitted by flying-squirrel ectoparasites is a milder illness; whether this milder disease is due to host factors (e.g., better health status) or organism factors (e.g., attenuated virulence) is unknown.

**Prevention** Prevention of epidemic typhus involves control of body lice. Clothes should be changed regularly, and insecticides should be used every 6 weeks to control the louse population.

**Diagnosis and Treatment** See Table 177-2. Epidemic typhus is sometimes misdiagnosed as typhoid fever in tropical countries.

## SCRUB TYPHUS

The etiologic agent of scrub typhus is a small, obligately intracellular bacterium of the family Rickettsiaceae that differs substantially from other family members in its genetic makeup and in the composition of its cell wall (which, for example, lacks lipopolysaccharide and peptidoglycan). Consequently, this organism has been classified as a species in a separate genus, *Orientia tsutsugamushi*.

*O. tsutsugamushi* is maintained in nature by transovarian transmission in trombiculid mites, mainly of the genus *Leptotrombidium*. After hatching, infected larval mites (chiggers, the only stage that feeds on an animal host) inoculate organisms into the skin while feeding. Scrub typhus is found in environments that harbor the infected chiggers, particularly areas of heavy scrub vegetation -- e.g., where the forest is regrowing after being cleared and along riverbanks. Infections occur during the wet season, when the mites lay their eggs. The disease is endemic in eastern and southern Asia, northern Australia, and islands of the western Pacific Ocean. Scrub typhus is also found in tropical areas of India, Sri Lanka, Bangladesh, Myanmar, Thailand, Malaysia, Laos, Vietnam, Kampuchea, China, Taiwan, the Philippines, Indonesia, Papua New Guinea, northern Australia, and islands of the South Pacific Ocean; in temperate areas of Japan, Korea, far-eastern Russia, Tadzhikistan, the mountains of northern India, Pakistan, and Nepal; and in nontropical areas of China, such as Tibet and Shangdong Province. Those infected include indigenous rural workers, residents of suburban areas, and westerners visiting endemic areas for professional or recreational purposes. Infections are more prevalent than the number of clinical diagnoses would suggest; in some areas more than 3% of the population is infected or reinfected each month. Immunity wanes over 1 to 3 years, and there is remarkable antigenic diversity.

**Clinical Manifestations** The illness varies in severity from mild and self-limiting to fatal. After an incubation period of 6 to 21 days (usually 8 to 10 days), the onset of disease is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. Some patients develop no further signs or symptoms and recover spontaneously after a few days. The classic case description includes an eschar at the site of chigger feeding, regional lymphadenopathy, and a maculopapular rash -- signs that are seldom observed in indigenous patients. Fewer than 50% of westerners develop an eschar, and fewer than 40% develop a rash (on day 4 to 6 of illness). Severe cases typically include prominent encephalitis and interstitial pneumonia as key features of vascular injury. Severe illness in persons withG6PDdeficiency has been accompanied by hemolysis. The case-fatality rate for untreated classic cases is 7% but would probably be lower if all relatively mild cases (which are underdiagnosed) were included.

**Diagnosis and Treatment** SeeTable 177-2. One report has described cases of scrub typhus in Thailand that do not respond to treatment with doxycycline or

chloramphenicol.

## EHRLICHIOSES

Ehrlichiae are small, obligately intracellular bacteria with a gram-negative-type cell wall that grow in cytoplasmic vacuoles to form clusters called *morulae* (Fig. 177-1). Two distinct *Ehrlichia* species cause human infections that can be severe and frequent (Table 177-3). *E. chaffeensis*, the agent of human monocytotropic ehrlichiosis (HME), infects predominantly mononuclear phagocytic cells in tissues and blood monocytes. A member of the *E. phagocytophila* group that infects cells of myeloid lineage is the agent of human granulocytotropic ehrlichiosis (HGE). Both *E. chaffeensis* and *E. phagocytophila* are tick-borne but are transmitted by distinct vectors with little geographic overlap. *E. ewingii* is a newly recognized agent of human ehrlichiosis. Identified in four patients to date by means of a broad-rangePCRassay, *E. ewingii* has previously been reported as a cause of granulocytotropic ehrlichiosis in dogs.

Ehrlichiae were discovered by veterinarians during the investigation of hemolytic anemia of cattle before 1910. Researchers thereafter discerned that "marginal points" within erythrocytes were infectious and named the agent *Anaplasma marginale*. Subsequently, several other species now known as ehrlichiae were detected as veterinary infectious agents, including *Cowdria ruminantium*, *E. canis*, *E. phagocytophila*, and *E. risticii*. In 1953, *E. sennetsu* was identified in humans with mononucleosis-like syndromes in Japan.

The current taxonomic positions are determined by nucleic acid sequences of conserved and unique genes among these species. By analysis of 16S ribosomal RNA sequences, the genus and related organisms can be divided into two major clades: the *E. canis* group (including *E. chaffeensis*) and the *E. phagocytophila* group (including *E. equi* and the agent ofHGE). The *E. sennetsu* group is as distantly related to both of these clades as it is to the genus *Rickettsia* and is not tick-borne. Given the lack of transovarian transmission in ticks, the natural maintenance of the tick-borne ehrlichiae clearly depends in part upon transient or persistent infections in wild and feral mammalian reservoirs. Thus, these bacteria are propagated by horizontal transmission that relies upon a tick-mammal-tick cycle; humans are inadvertently infected when they impinge upon the natural habitats occupied by the ticks and the reservoir hosts.

### HUMAN MONOCYTOTROPIC EHRLICHIOSIS

**Epidemiology** Infections caused by *E. chaffeensis* have been documented in more than 500 cases reported to the Centers for Disease Control and Prevention (CDC). However, sinceHME is not a reportable disease in most states, this figure is a gross underestimate. Most infections have been identified in the south-central, southeastern, and mid-Atlantic states, but cases have also been recognized in California, the Pacific northwest, New England, Europe, and Africa. The vector is the Lone Star tick (*Amblyomma americanum*), which in all its life stages feeds upon white-tailed deer, a major reservoir host. Dogs have been discovered to be subclinically infected and may also be an important reservoir. Tick bites and exposures are reported by patients, frequently in rural areas and especially in the months May through July. The median age of HME patients is 44 years, and 75% of the affected individuals are male; however,

severe and fatal infections in children are also well recognized.

**Clinical Manifestations** *E. chaffeensis* is inoculated into the dermal blood pool created by the feeding tick and subsequently disseminates via the blood to tissues. After a median incubation period of 8 days, illness develops; only about one-third of individuals who seroconvert develop a consistent clinical illness. The classic clinical manifestations are not specific and include fever (97% of cases), headache (81%), myalgia (68%), and malaise (84%); less frequently observed are gastrointestinal involvement (nausea, vomiting, diarrhea; 25 to 68%), cough (25%), rash (36% overall, 6% at presentation) (Fig. 177-CD7), and confusion (20%).HME may be severe: 62% of patients with documented cases are hospitalized, and about 2% die. Severe complications include a toxic shock-like or septic shock-like syndrome, respiratory insufficiency and adult respiratory distress, meningoencephalitis, fulminant infection (in immunocompromised patients), severe opportunistic and nosocomial infections, and hemorrhage. Laboratory findings may be of value in the differential diagnosis; 60 to 74% of patients with HME have leukopenia (initially lymphopenia, later neutropenia), 72% have thrombocytopenia, and nearly 90% have elevations in serum levels of hepatic aminotransferases. With effective therapy, rebound lymphocytosis is common. In spite of abnormal blood counts, examinations reveal hypercellular bone marrow, and noncaseating granulomas may be present. Vasculitis is not a component of HME.

**Diagnosis** BecauseHME can be rapidly fatal, empirical antibiotic therapy should be instituted on the basis of a clinical diagnosis. This diagnosis may be suggested by fever in the setting of known tick exposure during the preceding 3 weeks, leukopenia and/or thrombocytopenia, and increased aminotransferase concentrations in serum. Morulae are rarely demonstrated in peripheral blood smears unless an intensive examination is performed; even then, an experienced microscopist is required. The active phase of HME may be diagnosed byPCRamplification of *E. chaffeensis* nucleic acids from EDTA-anticoagulated blood obtained before the start of doxycycline therapy. Retrospective serologic diagnosis requires a consistent clinical picture and detection of a fourfold increase in *E. chaffeensis* antibody titer (to$^{3}$1:64) by indirect immunofluorescence in paired serum samples obtained approximately 30 days apart. It must be underscored that separate specific diagnostic tests for HME andHGE are necessary.

## TREATMENT

Tetracycline is effective therapy forHME. Either tetracycline (250 to 500 mg given orally every 6 h) or doxycycline (100 mg given orally or intravenously twice daily) is associated with a lowered rate of hospitalization and a shortened duration of fever. The use of chloramphenicol is controversial, and *E. chaffeensis* is not susceptible to this drug in vitro. While a few reports document the persistence of *E. chaffeensis* in humans after the acute phase of illness, such persistence is very infrequent; most patients are cured after relatively short courses of tetracycline therapy (continuing for 3 to 5 days after defervescence).

**Prevention** HME is prevented by the avoidance of ticks in endemic areas. The use of protective clothing and tick repellents, careful tick searches after exposures, and prompt removal of attached ticks markedly diminish risk.

## HUMAN GRANULOCYTOTROPIC EHRLICHIOSIS

**Epidemiology** As of 1995, approximately 150 cases ofHGE had been documented in 11 states (mostly in the upper midwest and the northeast), with a distribution similar to that of Lyme disease. Most cases have been identified within the range of various *I. ricinus*-complex ticks, particularly *I. scapularis*. White-footed deer mice in the United States and red deer in Europe appear to play a role in maintaining HGE in nature. The incidence of HGE peaks in May, June, and July, but the disease may occur throughout the year in conjunction with human exposure to *Ixodes* ticks. HGE affects predominantly males (79%) and older persons (median age, 58 years).

**Clinical Manifestations** Because of high seroprevalence rates in endemic regions, it seems likely that only a minority of infected individuals develop clinical manifestations. The incubation period forHGEvaries between 4 and 8 days, and the disease manifests as fever (94 to 100% of cases), myalgia (78 to 98%), headache (61 to 85%), and malaise (98%) -- findings suggestive of an influenza-like illness. A minority of patients develop gastrointestinal involvement, including nausea, vomiting, or diarrhea (22 to 39%); rash (2 to 11%); cough (27%); and confusion (17%). Severe complications occur most often in the elderly, but even children may be severely affected. Respiratory insufficiency, with adult respiratory distress syndrome, a toxic shock-like syndrome, and life-threatening opportunistic infections, are the most worrisome complications. Meningoencephalitis has not yet been conclusively recognized with HGE. The case-fatality rate is probably <1%, but nearly 7% of ill patients may require intensive care. As inHME, laboratory findings are of great assistance; most patients develop leukopenia and/or thrombocytopenia with increased serum levels of hepatic aminotransferases. The pancytopenia observed in HGE presumably relates to sequestration or destruction of platelets and leukocytes, since the bone marrow is ordinarily normo- or hypercellular. Vasculitis is not a component of HGE. Unlike HME, HGE is not associated with granulomas. While clear evidence exists for co-infections with *Borrelia burgdorferi* and *Babesia microti*, which are transmitted by the same tick vector(s), there is little evidence of comorbidity or of a persistent or chronic phase for HGE.

**Diagnosis** HGEshould be included in the differential diagnosis for patients who have been exposed to ticks and who develop an influenza-like illness during the season of *Ixodes* tick activity (May through December). The concurrent detection of thrombocytopenia, leukopenia, and/or elevations in serum aminotransferase activities further increases the likelihood of HGE. A substantial proportion of patients with HGE develop serologic reactions considered diagnostic of Lyme disease in the absence of clear clinical findings consistent with that diagnosis. Thus, HGE should be considered in the differential diagnosis of atypical severe presentations of Lyme disease. Although not highly sensitive, a thorough peripheral blood film examination for morulae in neutrophils may identify 20 to 75% of infections.PCR on EDTA-anticoagulated blood collected before initiation of tetracycline therapy from patients with active disease is a sensitive and specific method for early confirmation. Serodiagnosis is based mostly upon the retrospective demonstration of a fourfold increase in *E. phagocytophila* group antibody titer to a minimum of 1:80 in paired sera obtained approximately 1 month apart. IgM antibodies may be detected in many patients within the first 1.5 months after illness.

Approximately 15 to 40% of infected persons have a detectable antibody titer at presentation, but, in regions where seroprevalence is high, a single acute-phase polyvalent titer may be misleading.

**TREATMENT**

Doxycycline (100 mg given orally twice daily) is an effective therapeutic agent, while rifampin has been associated with clinical improvement in pregnant patients withHGE. In vitro studies suggest a role for trovafloxacin, but no prospective studies of any therapy for HGE have been conducted. Most treated patients defervesce within 24 to 48 h.

**Prevention** Prevention ofHGErequires tick avoidance. The Lyme disease vaccine offers no protection against HGE, and no other vaccine is available.

## Q FEVER

Q fever results from infection with *C. burnetii*. This small gram-negative microorganism (0.2 um by 0.7 um) exists in two antigenic forms: phase I and phase II. When *C. burnetii* is passaged in cell cultures or embryonated eggs, its lipopolysaccharide undergoes truncation that results in an antigenic change called *phase variation*. The phase I form is extremely infectious and exists in humans and other animals. Passage in cell culture or embryonated eggs results in a shift to the phase II form, which is avirulent. The ability of *C. burnetii* to form spores allows the organism to survive in harsh environments. Indeed, it can survive for more than 40 months in skim milk at room temperature and is readily recovered from soil up to 1 month after contamination. Three different plasmids have been described in various isolates of *C. burnetii*. Q fever encompasses two broad clinical syndromes: acute and chronic infection. It is likely that the host's immune response (rather than characteristics of the infecting strain) determines whether or not chronic Q fever develops.

**Epidemiology** Q fever is a zoonosis. The primary sources of human infection are infected cattle, sheep, and goats. However, infected cats, rabbits, and dogs have also been shown to transmit *C. burnetii* to humans. The extensive wildlife reservoir for *C. burnetii* includes mammals, birds, and ticks. In the infected female mammal, *C. burnetii* localizes to the uterus and the mammary glands. Infection is reactivated during pregnancy, and high concentrations of *C. burnetii* are found in the placenta. At parturition, *C. burnetii* is dispersed as an aerosol, and infection follows inhalation of aerosolized organisms by a susceptible host. Infected female animals shed the organism in milk for weeks to months after parturition. In rare instances, human-to-human transmission has followed delivery of an infant to an infected woman or autopsy on an infected individual. *C. burnetii* has been transmitted via blood transfusion. Those at risk for Q fever are abattoir workers, veterinarians, and other individuals who vocationally or avocationally come into contact with infected animals. Exposure to infected newborn animals or to infected products of conception poses the highest risk. Sexual transmission has been demonstrated experimentally in mice, as has transmission during artificial insemination in cattle. Whether *C. burnetii* is sexually transmitted among humans is not yet known. While the experimental evidence on this point is contradictory, the ingestion of contaminated milk in some areas is probably a

major route of transmission to humans.

Infections due to *C. burnetii* occur in most countries. Indeed, the only areas known to be free of *C. burnetii* are New Zealand and Antarctica. The primary manifestation of acute Q fever differs from place to place: It is pneumonia in Nova Scotia (Canada) and granulomatous hepatitis in Marseille (France), while both of these manifestations are seen in the Basque country of Spain. These differences may reflect the route of infection; i.e., the ingestion of contaminated milk may result in hepatitis and the inhalation of contaminated aerosols in pneumonia.

**Clinical Manifestations**

*Acute Q Fever* The incubation period for acute Q fever ranges from 3 to 30 days. The clinical presentations include flulike syndromes, prolonged fever, pneumonia, hepatitis, pericarditis, myocarditis, meningoencephalitis, and infection during pregnancy. The symptoms of acute Q fever are nonspecific; common among them are fever, extreme fatigue, and severe headache. Other symptoms include chills, sweats, nausea, vomiting, and diarrhea, which occur in 5 to 20% of patients. Cough develops in about half of patients with Q fever pneumonia. Neurologic manifestations of acute Q fever are uncommon; however, in one outbreak in the West Midlands, United Kingdom, 23% of 102 patients had neurologic signs and symptoms as the major manifestation. A nonspecific rash may be evident in 4 to 18% of patients. The white blood cell count is usually normal. Thrombocytopenia is detected in about 25% of patients, and reactive thrombocytosis [with platelet counts of up to 1 million/uL ($1 \times 10^{12}$/L)] frequently develops during recovery. This thrombocytosis may account for cases of deep vein thrombophlebitis complicating acute Q fever in some series. Uncommon manifestations of acute Q fever include optic neuritis, extrapyramidal neurologic disease, Guillain-Barre syndrome, inappropriate secretion of antidiuretic hormone, epididymitis, orchitis, priapism, hemolytic anemia, mediastinal lymphadenopathy mimicking lymphoma, pancreatitis, erythema nodosum, and mesenteric panniculitis. Chest radiography may show an opacity that is indistinguishable from those seen in pneumonia of other etiologies (Fig. 177-CD8). Multiple rounded opacities are common; in the appropriate epidemiologic setting, they are highly suggestive of Q fever pneumonia. However, right-sided endocarditis resulting in septic pulmonary emboli can produce the same radiographic appearance.

*Chronic Q Fever* Chronic Q fever, which is uncommon, almost always implies endocarditis. This infection usually occurs in patients with previous valvular heart disease, immunosuppression, or chronic renal insufficiency. Fever is usually absent or low grade. Patients may have nonspecific symptoms for up to 1 year before diagnosis. Valvular vegetations have been seen in only 12% of patients with transthoracic echocardiograms, but the rate of detection may be higher with the use of transesophageal echocardiography. A high index of suspicion is necessary for a correct diagnosis. The disease should be suspected in all patients with culture-negative endocarditis. In addition, all patients with valvular heart disease and an unexplained purpuric eruption, renal insufficiency, stroke, and/or progressive heart failure should be tested for *C. burnetii* infection. Patients with chronic Q fever have hepatomegaly and/or splenomegaly. These two findings, especially in combination with positive rheumatoid factor, high erythrocyte sedimentation rate, high C-reactive protein level, and/or

increased g-globulin concentrations (up to 60 to 70 g/L), suggest this diagnosis. Other manifestations of chronic Q fever include infection of vascular prostheses, aneurysms, and bone.

**Diagnosis** *C. burnetii* can be isolated from buffy-coat blood samples or tissue specimens by a shell-vial technique; however, most laboratories are not permitted to attempt the isolation of *C. burnetii* since it is considered highly infectious.PCR can be used to amplify *C. burnetii* DNA from tissue or biopsy specimens. This technique can also be used on paraffin-embedded tissues. Serology, however, is the most commonly used diagnostic tool. Three techniques are available: complement fixation, indirect immunofluorescence, and enzyme-linked immunosorbent assay. Indirect immunofluorescence is sensitive and specific and is the method of choice. Rheumatoid factor should be adsorbed from the specimen before testing. An IgG titer of ³1:800 to phase I antigen is suggestive of chronic Q fever. In almost all instances of chronic Q fever, the antibody titer to phase I antigen is much higher than that to phase II antigen. The reverse is true in acute Q fever. In addition, in acute Q fever, it is usually possible to demonstrate a fourfold rise in titer between acute- and convalescent-phase serum samples.

## TREATMENT

Treatment of acute Q fever with doxycycline (100 mg twice daily for 14 days) is usually successful. Quinolones are also effective. Treatment of chronic Q fever should include at least two antibiotics active against *C. burnetii*. The combination of rifampin and doxycycline has been used with success. For chronic infection, doxycycline should be given as 100 mg twice daily and rifampin as 300 mg once daily. The optimal duration of antibiotic therapy for chronic Q fever remains undetermined. We recommend a minimum of 3 years of treatment, with discontinuation only if the phase I IgA antibody titer is£1:50 and the IgG phase I titer is£1:200. Another therapeutic option under investigation is the combination of doxycycline (100 mg twice daily) with hydroxychloroquine (600 mg once daily). With this combination, therapy can be completed in 18 months. It is necessary to monitor hydroxychloroquine levels and to adjust the dosage to maintain a plasma concentration of 0.8 to 1.2 ug/mL. In vitro, the addition of 1 mg of hydroxychloroquine/mL renders doxycycline bactericidal for *C. burnetii*.

**Prevention** A vaccine has been shown to be effective in preventing Q fever in abattoir workers in Australia.

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Back to Table of Contents

# 178. *MYCOPLASMA* INFECTIONS - *William M. McCormack*

Mycoplasmas, the smallest free-living organisms known, are prokaryotes that are bounded only by a plasma membrane. Their lack of a cell wall is associated with cellular pleomorphism and resistance to cell wall-active antimicrobial agents, such as penicillins and cephalosporins. The organisms' small genome limits biosynthesis and explains the difficulties encountered with in vitro cultivation. Mycoplasmas typically colonize mucosal surfaces of the respiratory and urogenital tracts of many animal species. Sixteen species of mycoplasmas have been recovered from humans. Most are commensals. *Mycoplasma pneumoniae* causes upper and lower respiratory tract infections. *M. genitalium* and *Ureaplasma urealyticum* are established causes of urethritis and have been implicated in other genital conditions. *M. hominis* and *U. urealyticum* are part of the complex microbial flora of bacterial vaginosis.

## MECHANISMS OF PATHOGENICITY

Adherence of mycoplasmas to the surface of the host cell is necessary for colonization and infection. Some pathogenic mycoplasmas are flask-shaped, with specialized tips that enhance adherence. *M. pneumoniae* adheres via a network of interactive adhesins and accessory proteins and produces hydrogen peroxide, which may cause injury to host cells. *M. hominis* metabolizes arginine, with the production of potentially cytotoxic amounts of ammonia. Ureaplasmas have been placed in a separate genus because of their unique urease activity; the metabolism of urea also produces ammonia. *M. pneumoniae* may evoke IgM autoantibodies that agglutinate human erythrocytes at 4°C. These cold agglutinins can cause anemia and other complications (Fig. 178-CD1).

## *MYCOPLASMA PNEUMONIAE*

### EPIDEMIOLOGY

*M. pneumoniae* causes upper and lower respiratory tract symptoms in all age groups, with the highest attack rates in 5- to 20-year-olds. The infection is acquired by inhalation of aerosols. The incubation period is 2 to 3 weeks, considerably longer than that of most other respiratory infections. Although epidemics have taken place in closed populations, such as schools and military installations, most cases occur sporadically or in families. In families, cases typically occur serially, with 2- to 3-week intervals between cases. Infections in adults are often the result of contact with children.

Infection with *M. pneumoniae* is worldwide. Cases occur throughout the year, with epidemics every few years. Some studies have noted an increase in the number of cases during the autumn months in temperate climates. Although pneumonia is the classic presentation, nonpneumonic infection is considerably more common. In very young children, most infections result only in upper respiratory symptoms, whereas children>5 and adults may have bronchitis and pneumonia.

### CLINICAL PRESENTATION

After a prolonged incubation period, fever and constitutional symptoms develop along with headache and cough, both of which can be prominent and distressing. Symptoms

typically progress less rapidly than those of viral respiratory tract infections. In the minority (perhaps 5 to 10%) of infected individuals who develop tracheobronchitis or pneumonia, cough becomes more prominent. Sputum, if produced at all, is usually white and may be tinged with blood. The temperature seldom rises above 38.9 to 39.4°C (102 to 103°F). Shaking chills, myalgias, and gastrointestinal symptoms (e.g., nausea, vomiting, and diarrhea) are unusual. Chest muscle soreness may result from frequent and prolonged coughing, but true pleuritic pain is uncommon.

Pharyngeal injection is often noted. Cervical lymph node enlargement is unusual. Bullous myringitis is a unique but uncommon manifestation. As in other "atypical" pneumonias, findings on auscultation of the lung may be normal or nearly normal despite striking radiographic abnormalities. Pleural effusions develop in<20% of patients.

*M. pneumoniae* infection may be particularly severe in patients who have sickle cell disease and other hemoglobin S-related hemoglobinopathies. The functional asplenia seen in sickle cell disease may contribute to severe mycoplasmal disease as it does in pneumococcal infection. Severe respiratory distress and large pleural effusions may occur. Digital necrosis has been seen in patients with sickle cell disease who develop very high titers of cold agglutinins.

**EXTRAPULMONARY MANIFESTATIONS**

A broad array of extrapulmonary abnormalities have been associated with *M. pneumoniae* infection. Although these events are unusual, they complicate other respiratory diseases even more rarely and often provide the only clue that an otherwise unremarkable respiratory infection may be mycoplasmal.

Erythema multiforme (Stevens-Johnson syndrome; see Plate IIE-67) typically occurs in young male patients with *M. pneumoniae* infection. Other dermatologic manifestations, such as maculopapular and vesicular exanthems, erythema nodosum, and urticaria, have been reported, but none is as clearly linked to *M. pneumoniae* as is erythema multiforme.

Cardiac abnormalities reported in conjunction with *M. pneumoniae* infection include myocarditis and pericarditis, which may result in abnormalities of conduction. Of the wide variety of neurologic conditions associated with *M. pneumoniae*, most have been documented in case reports, where establishment of a cause-and-effect relationship is problematic. Central nervous system abnormalities that have been associated with *M. pneumoniae* include encephalitis, cerebellar ataxia, Guillain-Barre syndrome, transverse myelitis, and peripheral neuropathies. Arthralgias are not unusual in patients who have mycoplasmal pneumonia; mycoplasmal arthritis is rare except in patients who have hypogammaglobulinemia. Hematologic abnormalities associated with *M. pneumoniae* include hemolytic anemia and coagulopathies.

The pathogenesis of the extrapulmonary manifestations of *M. pneumoniae* infection is controversial. Occasional reports have described the identification of *M. pneumoniae* or its nucleic acids in involved tissues. The fact that most attempts at detection have been negative, however, suggests that these extrapulmonary complications have an

immunologic basis. Mycoplasmas, including *M. pneumoniae*, can nonspecifically stimulate B lymphocytes. *M. pneumoniae*-infected individuals can develop autoantibodies, including those reactive with brain, heart, and muscle.

## DIAGNOSIS

Most infections with *M. pneumoniae* are not diagnosed, as they are indistinguishable from upper and lower respiratory tract infections caused by myriad other viral and bacterial pathogens. When the diagnosis is suspected, it is usually because illness is prolonged or extrapulmonary manifestations develop. The white blood cell count is generally somewhat elevated, with few immature cells. Gram's stain of sputum shows leukocytes without a predominance of any bacterial morphologic type. Since *M. pneumoniae* lacks a cell wall, it cannot be detected on Gram's stain. In patients who have pneumonia, the chest radiograph may show reticulonodular or interstitial infiltration, primarily in the lower lobes. As in other "atypical" pneumonias, radiographic abnormalities may be more prominent than would be predicted by auscultation of the chest.

*M. pneumoniae* can be grown on artificial media, but the process is exacting, requires special media, and takes upwards of 2 weeks. Thus, mycoplasmal cultures do not provide timely information to aid in patient management. The same, unfortunately, is true of serologic diagnosis. Specific antibodies can be detected by enzyme-linked immunoassays, indirect immunofluorescence, or complement fixation but do not develop early enough to guide decisions regarding treatment. As with most serologic tests, examination of paired acute- and convalescent-phase serum specimens is required for good sensitivity and specificity.

Cold agglutinins are nonspecific but develop within the first 7 to 10 days in more than half of patients with *M. pneumoniae* pneumonia and may be detectable when the patient presents to a health care provider. In a patient with a compatible clinical picture, a cold agglutinin titer of³1:32 supports the diagnosis of mycoplasmal pneumonia. Cold agglutinin determinations are readily available from diagnostic laboratories. The test can also be performed at the bedside by the addition of 1 mL of the patient's blood to a tube containing anticoagulant (e.g., a tube used to collect blood for determination of prothrombin activity). Before cooling, the nonaggregated red blood cells coat the sides of the inverted tube. The blood is cooled to 4°C when the tube is placed in an ice bath for 3 to 5 min or in a standard refrigerator. In a positive test, clumps of red blood cells can be observed when the tube is inverted. Rewarming of the sample to 37°C in an incubator or by exposure to body heat should reverse the agglutination. A positive "bedside" cold agglutinin test is equivalent to a laboratory titer of³1:64.

The lack of sensitive, specific, and timely diagnostic tests has prompted the development of a variety of antigen detection tests that do not involve serology or the cultivation of live organisms. Such tests include antigen capture, indirect enzyme immunoassays, DNA probing, and nucleic acid amplification. Since many viral and bacterial infections result in clinical presentations similar to that caused by *M. pneumoniae*, examination of specimens for single antigens is unlikely to be useful. Rather, tests that examine an individual specimen for multiple antigens are needed. Multiplex nucleic acid amplification tests that examine a single throat swab or sputum

sample for all of the most likely causative microorganisms are feasible with current technology. Prototype multiplex polymerase chain reaction (PCR) assays have already been developed. If such tests become available clinically, more precise etiologic diagnosis of upper and lower respiratory tract infections will be possible.

### TREATMENT

Because most mycoplasmal infections are not specifically diagnosed, management is directed at one of two syndromes: upper respiratory tract infection or community-acquired pneumonia. Upper respiratory infections, whether caused by viruses or by *M. pneumoniae*, do not require antimicrobial treatment. Community-acquired pneumonia (Chap. 255) may be caused by bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* or by "atypical" agents such as *Chlamydia pneumoniae*, *Legionella pneumophila*, and *M. pneumoniae*. Recommended treatment regimens include a third-generation cephalosporin, such as intravenous ceftriaxone (1.0 g/d) or cefotaxime (1.0 g every 8 h), that is active against the conventional bacterial pathogens plus intravenous or oral erythromycin (500 mg four times a day) to cover atypical microorganisms. Newer agents that have antimicrobial activity against both conventional and atypical causes of community-acquired pneumonia may be prescribed as monotherapy. These drugs include oral clarithromycin (500 mg twice a day), intravenous or oral azithromycin (500 mg once daily), and intravenous or oral levofloxacin (500 mg once daily). Treatment of documented *M. pneumoniae* pneumonia is usually continued for 14 to 21 days.

Pneumonia due to *M. pneumoniae* is usually self-limited and is seldom life-threatening. Effective antimicrobial agents do shorten the duration of illness and, by reducing coughing, may conceivably render the patient less infectious. Although symptoms are alleviated by antimicrobial treatment, the organism usually is not eradicated. Cultures positive for *M. pneumoniae* may persist for months despite effective antimicrobial treatment. The beneficial effects, if any, of such treatment on extrapulmonary manifestations of *M. pneumoniae* infection are unknown.

## GENITAL MYCOPLASMAS (See also Chap. 132)

### EPIDEMIOLOGY

*M. hominis* and *U. urealyticum* are the most prevalent genital mycoplasmas. Infants may become colonized with one or both of these organisms during passage through a colonized birth canal. Neonatal colonization tends not to persist. Only about 10% of prepubertal girls and even fewer prepubertal boys are colonized with ureaplasmas. After puberty, colonization occurs mainly as a result of sexual activity. Among adults, disadvantaged populations have higher colonization rates. Ureaplasmas can be cultured from the vaginas of ~80% of women cared for in public clinics and about half of women cared for by private obstetricians and gynecologists. Similarly, vaginal *M. hominis* is found in 50% of women attending public clinics and in ~20% of private patients. Men have somewhat lower rates of genital colonization than women. Nonetheless, both *U. urealyticum* and *M. hominis* are frequently detected in genital specimens from healthy, sexually experienced adults. Evaluation of the role of these organisms in human disease must take into account their high prevalence among healthy people.

*M. fermentans* colonizes both the respiratory and genital tracts in>20% of adults. There is no convincing evidence that *M. fermentans* causes human disease; although it had been implicated as a possible determinant of HIV-1 disease progression, more recent data do not support such a role. *M. genitalium* is a fastidious organism that is difficult to cultivate.PCRstudies have identified the organism more successfully. Little is known about the epidemiology of *M. genitalium*.

## ASSOCIATION WITH HUMAN DISEASE

**Nongonococcal Urethritis** *Chlamydia trachomatis* is the organism most firmly implicated in the etiology of nongonococcal urethritis (NGU). There is no doubt that both *U. urealyticum* and *M. genitalium* also cause some cases of NGU. The ubiquity of ureaplasmas among men who do not have urethritis and the difficulty of identifying *M. genitalium* do not allow precise estimation of the proportion of cases of NGU caused by each of these mycoplasmas. *U. urealyticum* and *M. genitalium* do, however, appear to cause most of the nonchlamydial cases.

**Epididymitis and Prostatitis** Ureaplasmas may be an occasional cause of epididymitis. *M. hominis* has not been implicated in this disease. Neither organism has been convincingly associated with prostatitis.

**Pelvic Inflammatory Disease (PID) (See also Chap. 133)** *M. hominis* and *U. urealyticum* are both prominent components of the complex microbial flora of bacterial vaginosis. Since bacterial vaginosis is associated with PID, it is difficult to determine whether either organism plays an independent role in this condition. Although *M. genitalium* is not associated with bacterial vaginosis, preliminary studies have linked it to PID in women who are not infected with either *Neisseria gonorrhoeae* or *C. trachomatis*.

**Disorders of Reproduction** Ureaplasmas have been considered as causes of involuntary infertility in both men and women, but there is no convincing evidence for such an association. These organisms have been associated with chorioamnionitis and late abortion. Given the close association of ureaplasmas with bacterial vaginosis, a condition that is strongly associated with chorioamnionitis and late abortion, it is difficult to define an independent role for ureaplasmas in this condition. In infants of very low birthweight, ureaplasmas have been shown to cause pneumonia and chronic lung disease.

**Extragenital Infections** Sexually acquired reactive arthritis and Reiter's disease may be triggered by ureaplasmas, although *C. trachomatis* is the usual triggering agent. Patients who have hypogammaglobulinemia may develop chronic arthritis due to ureaplasmas and some other mycoplasmal species. *M. hominis* has been identified in patients with postthoracotomy sternal wound infection and in rare instances of prosthetic heart valve and prosthetic joint infection.

## DIAGNOSIS

There is seldom any reason to examine specimens from the lower genital tract (vagina, male urethra) for mycoplasmas. The ubiquity of the organisms among healthy

individuals makes a positive result uninterpretable. The organisms should be sought only in specimens from normally sterile areas, such as joint fluid with evidence of inflammation and cultures negative for conventional microorganisms.

*M. hominis* can replicate in many routine blood culture media without changing the appearance of the media. *M. hominis* forms nonhemolytic pinpoint colonies on blood agar; organisms cannot be visualized in gram-stained smears of these colonies. Neither *U. urealyticum* nor *M. genitalium* will grow in ordinary microbiologic media.

Microbiologic diagnosis of genital mycoplasmal infection requires specially prepared media and is beyond the capability of all but reference and research laboratories. Nucleic acid amplification tests such asPCR have been developed and may become commercially available.

**TREATMENT**

Ureaplasmas, *M. genitalium*, and *M. hominis* are usually susceptible to tetracyclines (e.g., doxycycline). Tetracycline-resistant ureaplasmas can be treated with erythromycin, while tetracycline-resistant strains of *M. hominis* respond to treatment with clindamycin. As noted above, a specific microbiologic diagnosis of mycoplasmal infection is seldom made. Appropriate treatment provides antimicrobial coverage for the organisms that cause the particular syndrome. Accordingly,NGU is treated with doxycycline (100 mg orally twice a day for 7 days) or azithromycin (1.0 g as a single oral dose) to provide activity against *C. trachomatis*, *U. urealyticum*, and *M. genitalium*. Recommended regimens for the treatment ofPIDprovide antimicrobial activity against gonococci, chlamydiae, and anaerobes as well as genital mycoplasmas.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 179. CHLAMYDIAL INFECTIONS - *Walter E. Stamm*

The genus *Chlamydia* contains three species that infect humans: *Chlamydia psittaci*, *C. trachomatis*, and *C. pneumoniae* (formerly the TWAR agent). *C. psittaci* is widely distributed in nature, producing genital, conjunctival, intestinal, or respiratory infections in many mammalian and avian species. Genital infections with *C. psittaci* have been well characterized in several species and cause abortion and infertility. Although mammalian strains of *C. psittaci* are not known to infect humans, avian strains occasionally do so, causing pneumonia and the systemic illness known as *psittacosis*.

*C. pneumoniae* is a fastidious chlamydial species that appears to be a common cause of upper respiratory tract infection and pneumonia, primarily in children and young adults, and is a cause of recurrent respiratory infections in older adults. Studies have also linked *C. pneumoniae* infection to atherosclerotic cardiovascular disease and perhaps to asthma and sarcoidosis. No animal reservoir has been identified for *C. pneumoniae*; it appears to be an exclusively human pathogen spread via the respiratory route through close personal contact. To date, all strains of *C. pneumoniae* studied have been serologically homologous.

*C. trachomatis* is also an exclusively human pathogen and was identified as the cause of trachoma in the 1940s. Since then, *C. trachomatis* has been recognized as a major cause of sexually transmitted and perinatal infection.

Chlamydiae are obligate intracellular bacteria that are classified in their own order (Chlamydiales). They possess both DNA and RNA, have a cell wall and ribosomes similar to those of gram-negative bacteria, and are inhibited by antibiotics such as tetracycline.

A unique feature of all chlamydiae is their complex reproductive cycle. Two forms of the microorganism -- the extracellular elementary body and the intracellular reticulate body -- participate in this cycle. The elementary body is adapted for extracellular survival and is the infective form transmitted from one person to another. Elementary bodies attach to susceptible target cells (usually columnar or transitional epithelial cells) and enter the cells inside a phagosome. Within 8 h of cell entry, the elementary bodies reorganize into reticulate bodies, which are adapted to intracellular survival and multiplication. They undergo binary fission, eventually producing numerous replicates contained within the intracellular membrane-bound "inclusion body," which occupies much of the infected host cell. Chlamydial inclusions resist lysosomal fusion until late in the developmental cycle. After 24 h, the reticulate bodies condense and form elementary bodies still contained within the inclusion. The inclusion then ruptures, releasing elementary bodies from the cell to initiate infection of adjacent cells or transmission to another person.

Studies with monoclonal antibodies to and nucleotide sequencing of the major outer-membrane protein have delineated at least 20 serotypes of *C. trachomatis*. According to the classification of Wang and Grayston, strains associated with trachoma have generally been those of the A, B, Ba, and C serovars, while serovars D through K have largely been associated with sexually transmitted and perinatally acquired infections. Serovars $L_1$, $L_2$, and $L_3$produce lymphogranuloma venereum (LGV) and hemorrhagic proctocolitis. The LGV strains demonstrate unique biologic behavior in that

they are more invasive than the other serovars, produce disease in lymphatic tissue, grow readily in cell culture systems and macrophages, and are fatal when inoculated intracerebrally into mice and monkeys. Non-LGV strains of *C. trachomatis* characteristically produce infections involving the superficial columnar epithelium of the eye, genitalia, and respiratory tract.

*C. trachomatis* has been reported as an infrequent cause of endocarditis, peritonitis, pleuritis, and possibly periappendicitis and may occasionally cause respiratory infections in older children and adults. Some immunosuppressed patients with pneumonia have had either serologic or cultural evidence of *C. trachomatis* infection, but more data are necessary to define a pathogenic role for *Chlamydia* in these patients.

## SEXUALLY TRANSMITTED AND PERINATAL INFECTIONS DUE TO *C. TRACHOMATIS*

### SPECTRUM OF *C. TRACHOMATIS* GENITAL INFECTIONS

Genital infections caused by *C. trachomatis* represent the most common bacterial sexually transmitted diseases (STDs) in the United States. An estimated 4 million cases occur each year. In adults, the clinical spectrum of sexually transmitted *C. trachomatis* infections parallels that of gonococcal infection. Both infections have been associated with urethritis, proctitis, and conjunctivitis in both sexes; with epididymitis in men; and with mucopurulent cervicitis (MPC) (Fig. 179-CD1), acute salpingitis, bartholinitis, and the Fitz-Hugh-Curtis syndrome (perihepatitis) in women. Moreover, both types of infection can be associated with septic arthritis. In general, however, chlamydial infections produce fewer symptoms and signs than corresponding gonococcal infections at the same anatomic site; in fact, chlamydial infections are often totally asymptomatic. Increasing evidence suggests that many chlamydial infections of the genital tract, especially in women, persist for months without producing symptoms. Simultaneous infection with *C. trachomatis* often occurs in women with cervical gonococcal infection and in heterosexual men with gonococcal urethritis.

### EPIDEMIOLOGY

Infections due to *C. trachomatis* are now reportable in the United States, and national incidence data show steadily rising numbers of reported infections, undoubtedly reflecting both increased testing and increased reporting. Most testing has focused upon women to date, and thus the reported incidence is severalfold greater in women than in men; this difference likely represents a surveillance artifact.

The age of peak incidence of genital *C. trachomatis* infections, as of other sexually transmitted infections, is the late teens and early twenties. The prevalence of chlamydial urethral infection among young men is at least 3 to 5% for those seen in general medical settings or in urban high schools,>10% for asymptomatic soldiers undergoing routine physical examination, and 15 to 20% for heterosexual men seen inSTDclinics. In areas where chlamydial control programs have been implemented, prevalence may be markedly reduced. In short, prevalence varies widely with the population group studied and with the geographic locale. The ratio of chlamydial to gonococcal urethritis is highest for heterosexual men and for those of high socioeconomic status and is lowest

for homosexual men and indigent populations.

The prevalence of cervical infection among women is approximately 5% for asymptomatic college students and prenatal patients in the United States, >10% for women seen in family planning clinics, and >20% for women seen inSTDclinics. As in men, prevalence varies substantially by geographic locale. However, substantial prevalences (~8%) of asymptomatic chlamydial infection were recently demonstrated in young female military recruits from all parts of the United States. In this country, the prevalence of *C. trachomatis* in the cervix of pregnant women is 5 to 10 times higher than that of *Neisseria gonorrhoeae.* The prevalence of genital infection with either agent is highest among individuals who are between the ages of 18 and 24, single, and non-Caucasian (e.g., black or hispanic). Recurrent chlamydial infections occur frequently in these same risk groups, often acquired from untreated sexual partners. Oral contraceptive pill use and the presence of cervical ectopy also confer an increased risk of chlamydial infection. The proportion of infections that are asymptomatic appears to be higher for *C. trachomatis* than for *N. gonorrhoeae*, and symptomatic *C. trachomatis* infections are clinically less severe. Mild or asymptomatic chlamydial infections of the fallopian tubes nonetheless cause ongoing tubal damage and infertility. Furthermore, because the total number of *C. trachomatis* infections exceeds the total number of *N. gonorrhoeae* infections in industrialized countries, the total morbidity caused by *C. trachomatis* genital infections in these countries equals or exceeds that caused by *N. gonorrhoeae*. The prevalence of *C. trachomatis* is higher than that of *N. gonorrhoeae* in industrialized countries, in part because measures such as treatment of sex partners and routine cultures for case detection in asymptomatic individuals have been applied much more effectively to the control of gonorrhea than to the control of *C. trachomatis* infection.

## PATHOGENESIS

*C. trachomatis* preferentially infects the columnar epithelium of the eye and the respiratory and genital tracts. The infection induces an immune response but often persists for months or years in the absence of antimicrobial therapy. Serious sequelae often occur in association with repeated or persistent infections. The precise mechanism through which repeated infection elicits an inflammatory response that leads to tubal scarring and damage in the female upper genital tract is not yet clear. One antigen, the chlamydial 60-kDa heat-shock protein, may be involved in inducing the pathologic immune response or may elicit antibodies that cross-react with human heat-shock proteins. The recent sequencing of the chlamydial genome may soon offer further insights into the pathogenic mechanisms of *C. trachomatis*.

## CLINICAL MANIFESTATIONS

**Nongonococcal and Postgonococcal Urethritis** Nongonococcal urethritis (NGU) is a diagnosis of exclusion that is applied to men with symptoms and/or signs of urethritis who do not have gonorrhea. Postgonococcal urethritis (PGU) refers to nongonococcal urethritis developing in men 2 to 3 weeks after treatment of gonococcal urethritis with single doses of agents such as amoxicillin or cephalosporins that lack sufficient activity against chlamydiae. Since current treatment regimens for gonorrhea also include tetracycline, doxycycline, or azithromycin for possible concomitant chlamydial infection,

both the incidence of PGU and the causative role of chlamydiae in this syndrome have declined. *C. trachomatis* causes 20 to 40% of cases of NGU in heterosexual men but is less commonly isolated from homosexual men with this syndrome. The cause of most of the remaining cases is uncertain; considerable evidence suggests that *Ureaplasma urealyticum* causes many cases of NGU, while *Trichomonas vaginalis* and herpes simplex virus (HSV) cause some cases.

NGUis diagnosed by documentation of a leukocytic urethral exudate and by exclusion of gonorrhea by Gram's staining or culture. *C. trachomatis* urethritis is generally less severe than gonococcal urethritis, although in an individual patient these two forms of urethritis cannot be reliably differentiated solely on clinical grounds. Symptoms include urethral discharge (often whitish and mucoid rather than frankly purulent), dysuria, and urethral itching. Physical examination may reveal meatal erythema and tenderness and a urethral exudate that is often demonstrable only by stripping of the urethra.

At least one-third of males with *C. trachomatis* urethral infection have no demonstrable signs or symptoms of urethritis. Use of nucleic acid amplification assays on first-void urine specimens to diagnose chlamydial infections in men has facilitated more broadly based testing for asymptomatic infection in males. As a result, asymptomatic chlamydial urethritis has been demonstrated in 5 to 10% of sexually active adolescent males screened in school-based clinics or community centers. Such patients generally have first-glass pyuria (³15 leukocytes per 400´ microscopic field in the sediment of first-void urine), a positive leukocyte esterase test, or an increased number of leukocytes on Gram-stained smear prepared from a urogenital swab inserted 1 to 2 cm into the anterior urethra. For the enumeration of leukocytes, the smear is first scanned at low power to identify areas of the slide containing the highest concentration of leukocytes. These areas are then examined under oil immersion (1000´). An average of four or more leukocytes in at least three of five 1000´ (oil-immersion) fields is indicative of urethritis and correlates with the recovery of *C. trachomatis*. To differentiate between true urethritis and functional symptoms among symptomatic patients or to make a presumptive diagnosis of *C. trachomatis* infection in a "high-risk" but asymptomatic man (e.g., male patients inSTDclinics, sex partners of women with nongonococcal salpingitis orMPC, fathers of children with inclusion conjunctivitis), the examination of an endourethral specimen for increased leukocytes is useful if specific diagnostic tests for chlamydiae are not available. Alternatively, noninvasive screening for urethritis can be accomplished by testing of a first-void urine sample for pyuria, either by microscopy or by the leukocyte esterase test. Urine can also be directly tested for chlamydiae or gonococci by DNA amplification methods, as described below.

**Epididymitis** *C. trachomatis* is the foremost cause of epididymitis in sexually active heterosexual men under 35 years of age, accounting for about 70% of cases. *N. gonorrhoeae* causes most of the remaining cases, and some men have simultaneous infections with both pathogens, usually accompanied by asymptomatic urethritis as defined above. In homosexual men, sexually transmitted coliform infection acquired via rectal intercourse may cause epididymitis. Coliform bacteria and *Pseudomonas aeruginosa*, usually in association with preceding urologic instrumentation or surgery, are the most common causes of epididymitis in men over 35. Men with epididymitis typically present with unilateral scrotal pain, fever, and epididymal tenderness or swelling on examination. The illness may be mild enough to treat on an outpatient basis

with oral antibiotics or severe enough to require hospitalization and parenteral therapy. Testicular torsion should be excluded promptly by radionuclide scan, Doppler flow study, or surgical exploration in a teenager or young adult who presents with acute unilateral testicular pain without urethritis. The possibility of testicular tumor or chronic infection (e.g., tuberculosis) should be excluded when a patient with unilateral intrascrotal pain and swelling does not respond to appropriate antimicrobial therapy.

**Reiter's Syndrome** Reiter's syndrome consists of conjunctivitis, urethritis (or cervicitis in females), arthritis, and characteristic mucocutaneous lesions (Chap. 315). *C. trachomatis* has been recovered from the urethra of up to 70% of men with untreated nondiarrheal Reiter's syndrome and associated urethritis. In the absence of overt urethritis, it is important to exclude subclinical urethritis in the men in whom this diagnosis is suspected.

The pathogenesis of Reiter's syndrome remains obscure. However, since more than 80% of affected patients have the HLA-B27 phenotype and since other mucosal infections (with *Salmonella*, *Shigella*, or *Campylobacter*, for example) produce an identical syndrome, chlamydial infection is thought to initiate an aberrant and hyperactive immune response that produces inflammation at the involved target organs in these genetically predisposed individuals. Evidence of exaggerated cell-mediated and humoral immune responses to chlamydial antigens in Reiter's syndrome supports this hypothesis. The presumptive demonstration of chlamydial elementary bodies and chlamydial DNA in the joint fluid and synovial tissue of patients with Reiter's syndrome suggests that chlamydiae may actually spread from genital to joint tissues in these patients, perhaps in macrophages.

**Proctitis** *C. trachomatis* strains of either the genital immunotypes D through K or theLGVimmunotypes cause proctitis in homosexual men who practice receptive anorectal intercourse. In the United States, the vast majority of cases are due to immunotypes D through K and present either as asymptomatic infection or as mild proctitis not unlike gonococcal proctitis. These infections may develop in heterosexual women as well. Patients present with mild rectal pain, mucous discharge, tenesmus, and (occasionally) bleeding. Nearly all have neutrophils in their rectal Gram's stain. Anoscopy in these non-LGV cases of chlamydial proctitis reveals mild, patchy mucosal friability and mucopurulent discharge, and the disease process is limited to the distal rectum. LGV strains produce more severe ulcerative proctitis or proctocolitis that can be confused clinically withHSVproctitis (severe rectal pain, bleeding, discharge, and tenesmus) and that histologically resembles Crohn's disease in that giant cell formation and granulomas can be seen (Chap. 287). In the United States, these cases occur almost exclusively in homosexual men.

**Mucopurulent Cervicitis** Although many women with *C. trachomatis* infection of the cervix have no symptoms or signs, a careful speculum examination reveals evidence ofMPC in 30 to 50% of cases. As is discussed more fully inChap. 133, MPC is associated with yellow mucopurulent discharge from the endocervical columnar epithelium and with³20 neutrophils per 1000´ microscopic field within strands of cervical mucus on a thinly smeared, Gram-stained preparation of endocervical exudate. Other characteristic findings include edema of the zone of cervical ectopy and a propensity of the mucosa to bleed on minor trauma -- e.g., when specimens are collected with a

swab. A Pap smear shows increased numbers of neutrophils as well as a characteristic pattern of mononuclear inflammatory cells, including plasma cells, transformed lymphocytes, and histiocytes. Cervical biopsy shows a predominantly mononuclear cell infiltrate of the subepithelial stroma, often with follicular cervicitis.

**Pelvic Inflammatory Disease (PID) (See alsoChap. 133)** *C. trachomatis* plays an important causative role in salpingitis. Infection with *C. trachomatis* has been demonstrated in laparoscopically verified salpingitis, the organism has been recovered from the fallopian tubes in the absence of other pathogens, and serologic evidence of recent *C. trachomatis* infection has been found in women with PID. In the United States, *C. trachomatis* has been identified in the fallopian tubes or endometrium of up to 50% of women with PID, and its role as an important etiologic agent in this syndrome is well accepted.

PIDoccurs via ascending intraluminal spread of *C. trachomatis* from the lower genital tract.MPC is thus followed by endometritis, endosalpingitis, and finally pelvic peritonitis. Evidence of MPC is usually found in women with laparoscopically verified salpingitis. Similarly, endometritis, demonstrated by endometrial biopsy showing plasma cell infiltration of the endometrial epithelium, is documented in most women with laparoscopically verified chlamydial (or gonococcal) salpingitis. Chlamydial endometritis can also occur in the absence of clinical evidence of salpingitis: approximately 40 to 50% of women with MPC have plasma cell endometritis. Histologic evidence of endometritis has been correlated with an "endometritis syndrome" consisting of vaginal bleeding, lower abdominal pain, and uterine tenderness in the absence of adnexal tenderness. It is not known what proportion of women who have chlamydial endometritis without adnexal tenderness also have salpingitis. However, chlamydial salpingitis produces milder symptoms than does gonococcal salpingitis and may be associated with less marked adnexal tenderness. Mild adnexal or uterine tenderness in sexually active women with cervicitis suggests PID.

Infertility associated with fallopian-tube scarring has been strongly linked to antecedent *C. trachomatis* infection in serologic studies. Since many infertile women with tubal scarring and antichlamydial antibody have no history ofPID, it appears that subclinical tubal infection ("silent salpingitis") may produce scarring. Studies in animals and humans with salpingitis and tubal scarring suggest the continuing presence of persistent, slowly replicating chlamydial infection in tubal tissue. Ectopic pregnancy, which occurs in more than 70,000 women in the United States annually, is also thought to be related to *Chlamydia*-induced tubal scarring in many cases. While the pathogenesis of *Chlamydia*-induced tubal scarring remains poorly understood, antibodies to the chlamydial 60-kDa heat-shock protein have been correlated with tubal infertility, ectopic pregnancy, and Fitz-Hugh-Curtis syndrome (see below). Thus this antigen may initiate an immune-mediated process that ultimately damages the fallopian tube. Host genetic susceptibility, as defined by HLA type, may also play an important role.

Perihepatitis, or the Fitz-Hugh-Curtis syndrome, was originally described as a complication of gonococcalPID. However, cultural and/or serologic evidence of *C. trachomatis* infection is found in three-quarters of women with this syndrome. *C. trachomatis* has also been cultured from exudate on the hepatic capsule in

laparoscopically verified cases. This syndrome should be suspected whenever a young, sexually active woman presents with an illness resembling cholecystitis (fever and right-upper-quadrant pain of subacute or acute onset). Symptoms and signs of salpingitis may be minimal. High titers of antibodies to *C. trachomatis* are generally present.

**Urethral Syndrome in Women** In the absence of infection with uropathogens such as coliforms or *Staphylococcus saprophyticus*, *C. trachomatis* is the pathogen most commonly isolated from college women with dysuria, frequency, and pyuria (Chap. 280). *Chlamydia* can also be isolated from the urethra of women without symptoms of urethritis, and up to 25% of femaleSTDclinic patients with chlamydial urogenital infection have cultures positive for *C. trachomatis* from the urethra only.

***C. trachomatis* Infection in Pregnancy** *C. trachomatis* in pregnancy has been associated in some studies (but not in others) with premature delivery and with postpartum endometritis. Whether these complications are in part attributable to *C. trachomatis* is not clear.

## PERINATAL INFECTIONS: INCLUSION CONJUNCTIVITIS AND PNEUMONIA

**Epidemiology** Studies in the United States have demonstrated that 5 to 25% of pregnant women have *C. trachomatis* infections of the cervix. In these studies, approximately one-half to two-thirds of children exposed during birth have acquired *C. trachomatis* infection. Roughly half of the infected infants (or 25% of the group exposed) have developed clinical evidence of inclusion conjunctivitis. In addition to infecting the eye, *C. trachomatis* has been isolated frequently and persistently from the nasopharynx, rectum, and vagina of such infants, occasionally for periods exceeding 1 year in the absence of treatment. Pneumonia develops in about 10% of children infected perinatally, and otitis media may in some cases result from perinatally acquired chlamydial infection.

**Inclusion Conjunctivitis of the Newborn (Neonatal Chlamydial Conjunctivitis)** Neonatal chlamydial conjunctivitis has an acute onset 5 to 14 days after birth and often produces a profuse mucopurulent discharge. However, it is impossible to differentiate chlamydial conjunctivitis from other forms of neonatal conjunctivitis (such as that due to *N. gonorrhoeae*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, orHSV) on clinical grounds; instead, laboratory diagnosis is required. Inclusions within epithelial cells are often detected in Giemsa-stained conjunctival smears, but these smears are considerably less sensitive than cultures, antigen detection tests, or nucleic acid hybridization tests for chlamydiae. Gram-stained smears may show gonococci or occasional small gram-negative coccobacilli in *Haemophilus* conjunctivitis, but smears should be accompanied by cultures for these agents.

**Infant Pneumonia** *C. trachomatis* causes a distinctive pneumonia syndrome in infants. Recent epidemiologic studies have linked chlamydial pulmonary infection in infants with increased occurrence of subacute lung disease (bronchitis, asthma, wheezing) in later childhood.

## LYMPHOGRANULOMA VENEREUM

**Definition** LGV is a sexually transmitted infection caused by *C. trachomatis* strains of the $L_1$, $L_2$, and $L_3$serovars. In the United States, most cases are caused by $L_2$organisms. Acute LGV in heterosexual men is characterized by a transient primary genital lesion followed by multilocular suppurative regional lymphadenopathy. Women, homosexual men, and -- in occasional instances -- heterosexual men may develop hemorrhagic proctitis with regional lymphadenitis. Acute LGV is almost always associated with systemic symptoms such as fever and leukocytosis but is rarely associated with systemic complications such as meningoencephalitis. After a latent period of years, late complications include genital elephantiasis due to lymphatic involvement; strictures; and fistulas of the penis, urethra, and rectum.

**Epidemiology** LGV is usually sexually transmitted, but occasional transmission by nonsexual personal contact, fomites, or laboratory accidents has been documented. Laboratory work involving the creation of aerosols of LGV organisms (e.g., sonication, homogenization) must be conducted only with appropriate measures for biologic containment.

The peak incidence ofLGVcorresponds to the age of greatest sexual activity: the second and third decades of life. The worldwide incidence of LGV is falling, but the disease is still endemic and a major cause of morbidity in Asia, Africa, South America, and parts of the Caribbean. In the Bahamas, an apparent outbreak of LGV has been described in association with a concurrent increase in heterosexual infection with HIV. However, only 186 cases were reported in the United States in 1995, for a rate of 0.1 case per 100,000 population.

The frequency of infection following exposure is believed to be much lower than that for gonorrhea and syphilis. Early manifestations are recognized far more often in men than in women, who usually present with late complications. In the United States, where the reported male-to-female ratio of cases is 3.4:1, most cases have involved homosexually active men and persons returning from abroad (travelers, sailors, and military personnel). The main reservoir of infection, although it has not been directly demonstrated, is presumed to be asymptomatically infected individuals.

**Clinical Manifestations** In heterosexuals, a *primary genital lesion* develops from 3 days to 3 weeks after exposure. It is a small, painless vesicle or nonindurated ulcer or papule located on the penis in men and on the labia, posterior vagina, or fourchette in women. The primary lesion is noticed by fewer than one-third of men withLGV and only rarely by women. It heals in a few days without scarring and, even when noticed, is usually recognized as LGV only in retrospect. LGV strains of *C. trachomatis* have occasionally been recovered from genital ulcers and from the urethra of men and the endocervix of women who present with inguinal adenopathy; these areas may be the primary site of infection in some cases.

In women and homosexual men, *primary anal* or *rectal infection* develops after receptive anorectal intercourse. In women, rectal infection withLGV (or non-LGV) strains of *C. trachomatis* presumably can also arise by the contiguous spread of infected secretions along the perineum (as in rectal gonococcal infections in women) or perhaps by spread to the rectum via the pelvic lymphatics.

From the site of the primary urethral, genital, anal, or rectal infection, the organism spreads via the regional lymphatics. Penile, vulvar, or anal infection can lead to inguinal and femoral lymphadenitis. Rectal infection produces hypogastric and deep iliac lymphadenitis. Upper vaginal or cervical infection results in enlargement of the obturator and iliac nodes.

The most common presenting picture in heterosexual men is the *inguinal syndrome*, which is characterized by painful inguinal lymphadenopathy beginning 2 to 6 weeks after presumed exposure; in rare instances, the onset comes after a few months. The inguinal adenopathy is unilateral in two-thirds of cases, and palpable enlargement of the iliac and femoral nodes is often evident on the same side as the enlarged inguinal nodes (Fig. 132-CD2). The nodes are initially discrete, but progressive periadenitis results in a matted mass of nodes that becomes fluctuant and suppurative. The overlying skin becomes fixed, inflamed, and thin and finally develops multiple draining fistulas. Extensive enlargement of chains of inguinal nodes above and below the inguinal ligament ("the sign of the groove") is not specific and, although not uncommon, is documented in only a minority of cases. On histologic examination, infected nodes are initially found to have characteristic small stellate abscesses surrounded by histiocytes. These abscesses coalesce to form large, necrotic, suppurative foci. Spontaneous healing usually takes place after several months; inguinal scars or granulomatous masses of various sizes persist for life. Massive pelvic lymphadenopathy in women or homosexual men may lead to exploratory laparotomy.

As cultures and serologic tests for *C. trachomatis* are being used more often, increasing numbers of cases ofLGVproctitis are being recognized in homosexual men. Such patients present with anorectal pain and mucopurulent, bloody rectal discharge. Although these patients may complain of diarrhea, they are often referring not to diarrhea but rather to frequent, painful, unsuccessful attempts at defecation (tenesmus). Sigmoidoscopy reveals ulcerative proctitis or proctocolitis, with purulent exudate and mucosal bleeding. The histopathologic findings in the rectal mucosa include granulomas with giant cells, crypt abscesses, and extensive inflammation. These clinical, sigmoidoscopic, and histopathologic findings may closely resemble those of Crohn's disease of the rectum.

Constitutional symptoms are common during the stage of regional lymphadenopathy and, in cases of proctitis, may include fever, chills, headache, meningismus, anorexia, myalgias, and arthralgias. These findings in the presence of lymphadenopathy are sometimes mistakenly interpreted as representing malignant lymphoma. Other systemic complications are infrequent but include arthritis with sterile effusion, aseptic meningitis, meningoencephalitis, conjunctivitis, hepatitis, and erythema nodosum. Chlamydiae have been recovered from the cerebrospinal fluid and in one case were isolated from the blood of a patient with severe constitutional symptoms -- a result indicating the dissemination of infection. Laboratory-acquired infections suspected of being due to the inhalation of aerosols have been associated with mediastinal lymphadenitis, pneumonitis, and pleural effusion.

Complications of untreated anorectal infection include perirectal abscess; fistula in ano; and rectovaginal, rectovesical, and ischiorectal fistulas. Secondary bacterial infection

probably contributes to these complications. Rectal stricture is a late complication of anorectal infection and usually develops 2 to 6 cm from the anal orifice -- i.e., at a site within reach on digital rectal examination. Proximal extension of the stricture for several centimeters may lead to a mistaken clinical and radiographic diagnosis of carcinoma.

A small percentage of cases ofLGV in men present as chronic progressive infiltrative, ulcerative, or fistular lesions of the penis, urethra, or scrotum. Associated lymphatic obstruction may produce elephantiasis. When urethral stricture occurs, it usually involves the posterior urethra and causes incontinence or difficulty with urination.

## APPROACH TO THE DIAGNOSIS AND TREATMENT OF *C. TRACHOMATIS* GENITAL INFECTIONS

Four types of laboratory procedure are available to confirm *C. trachomatis* infection: direct microscopic examination of tissue scrapings for typical intracytoplasmic inclusions or elementary bodies; isolation of the organism in cell culture; detection of chlamydial antigens or nucleic acid by immunologic or hybridization methods; and detection of antibody in serum or in local secretions.

Except in conjunctivitis, direct microscopic examination of Giemsa-stained cell scrapings for typical inclusions has an unacceptably low degree of sensitivity, and false-positive interpretations by inexperienced observers are common. Even for conjunctivitis, this approach has been replaced by direct fluorescent antibody staining of conjunctival smears to identify chlamydial elementary bodies with specific monoclonal antibodies (see below).

Cell culture techniques for isolation of *C. trachomatis* are available in most large medical centers but not in other clinical settings. In addition to limited availability, other disadvantages of cell culture include its low and variable level of sensitivity (60 to 80%), its requirement for rigorous transport conditions, and its high cost and technically demanding nature. Therefore, nonculture alternatives involving antigen detection or nucleic acid hybridization have been developed. In the direct immunofluorescent antibody (DFA) slide test, potentially infected genital or ocular secretions are smeared onto a slide, fixed, and stained with fluorescein-conjugated monoclonal antibody specific for chlamydial antigens. The observation of fluorescing elementary bodies confirms the diagnosis. Compared with culture, this test is 70 to 85% sensitive, and it is quite specific when used for confirmation of urethral, cervical, or ocular infection in high-risk patients with suspected *C. trachomatis* infection. The sensitivity and specificity of the test depend directly upon the skill of the microscopist. The apparently lower sensitivity of the test in low-risk populations, along with its relatively labor-intensive nature, limits its value as a screening tool.

Enzyme-linked immunosorbent assay (ELISA) techniques for the detection of chlamydial antigens provide another alternative to culture. The reported sensitivity and specificity of these tests for genital infections (as compared with culture) have been 60 to 80% and 97 to 99%, respectively, in high-risk populations. Sensitivities have generally been higher in cervical infection and lower in urethritis among males. Like theDFAslide test, the ELISA is less sensitive and less specific in low-prevalence populations and largely asymptomatic patients. ELISAs are better suited to screening

than is DFA because large numbers of specimens can easily be processed.

Assays with nucleic acid probes have also been developed for chlamydial diagnosis. One such test uses DNA-RNA hybridization and appears to be approximately equal to the bestELISAs in terms of sensitivity and specificity. Nucleic acid probes have also been developed for use in amplification assays such as ligase chain reaction and polymerase chain reaction (PCR). These tests are now the most sensitive chlamydial diagnostic methods available, being the first nonculture assays actually to surpass culture itself in sensitivity. In addition, the ability of these tests to detect chlamydial genes in urine with a high degree of sensitivity and specificity allows their use with urine specimens rather than with conventional urethral and cervical swabs for the first time. The use of urine specimens is particularly appealing for public-health chlamydial screening programs because of the ease of sample collection, even in community-based settings.

Serologic tests are of limited usefulness in the diagnosis of chlamydial oculogenital infections. The complement fixation test with heat-stable, genus-specific antigen has been used with some success to diagnoseLGV but is insensitive in infections due to non-LGV strains of *C. trachomatis*. The microimmunofluorescence (micro-IF) test with *C. trachomatis* antigens is more sensitive but is generally available only in research laboratories. The test measures antibodies by serovar specificity and by immunoglobulin class (IgM, IgG, IgA, secretory IgA) in both serum and local secretions. Serologic diagnosis by themicro-IFtest may be useful in infant pneumonia (in which high-titer IgM antibody and/or fourfold rises in titer are often demonstrated), in chlamydial salpingitis (especially Fitz-Hugh-Curtis syndrome), and in LGV. In all of these more invasive syndromes, high antibody levels are present.

Table 179-1 summarizes the diagnostic tests of choice for patients with suspected *C. trachomatis* infection. With few exceptions, the most suitable method for diagnosis is demonstration of the agent by either cell culture or one of the newer nonculture techniques. Selection of the most appropriate of these tests often depends upon local availability and expertise. However, it is clear that, in most settings and for most purposes, sensitivity and specificity will be greatest with nucleic acid amplification techniques. For patients to whom medicolegal considerations may apply (victims of sexual or child abuse), cultures or nucleic acid amplification methods should always be used. Since *C. trachomatis* is an intracellular pathogen, adequate specimens for chlamydial diagnostic testing must include epithelial cells. Cultures or nonculture tests of pus are less often positive. In urethritis, a thin-shafted urogenital swab should be inserted at least 2 cm into the urethra to obtain an appropriate specimen. Although cultures of urine for chlamydiae are less sensitive than urethral cultures, studies suggest that nucleic acid amplification testing of a first-void urine specimen from men is a more sensitive and less painful diagnostic alternative to the more invasive urethral swab-based tests, culture, or antigen detection tests. The first 30 mL of voided urine should be collected for testing. When a cervical sample is collected, the external os should first be cleaned of debris and purulent material; a plastic-shafted swab should then be inserted into the cervix, rotated slowly several times, and withdrawn. For the diagnosis of urogenital (cervical or urethral) infections in women, testing of a first-void urine specimen by nucleic acid amplification methods is at least as sensitive as testing of a cervical swab. When conjunctival specimens are sought, the epithelium should be

swabbed to remove cells rather than just purulent material. All specimens for chlamydial culture should be placed immediately into transport medium and then either refrigerated (if they will reach the laboratory within 12 to 18 h) or frozen at-70°C (if longer storage is anticipated). A major advantage of the nonculture diagnostic techniques is their less rigid transport requirements; neither refrigeration nor rapid transport is needed.

From a public health viewpoint, the most effective use of chlamydial diagnostic testing has not been unequivocally established and varies with the clinical population, local resources, and laboratory expertise. Since chlamydial diagnostic testing has become more widely available and is now more sensitive and specific than in the past, its use for specific diagnosis in patients with suspected chlamydial syndromes (such asMPC,NGU, andPID) and their partners should be promoted. High priority should be given to the screening of asymptomatic high-risk women who would not otherwise receive treatment for presumptive chlamydial infection, especially those seen in high-risk settings (e.g.,STDclinics or abortion clinics) and those with a high-risk profile (e.g., sexually active and £21 years of age, new sex partner within the preceding 2 months, or more than one current sex partner). Similar screening programs should be used to detect and treat asymptomatic urethritis in high-risk adolescent males. Where implemented, screening programs of this type have been associated with reductions in the prevalence of chlamydial infection and of its complications, such as PID.

## ANTIMICROBIAL SUSCEPTIBILITY

In laboratory tests that evaluate the growth of chlamydiae in cell cultures, the tetracyclines, erythromycin, rifampin, certain fluoroquinolones (especially ofloxacin), and the macrolide azithromycin are all highly active against these organisms. Sulfonamides and clindamycin are also active against *C. trachomatis*, but to a lesser degree. Penicillin and ampicillin suppress chlamydial multiplication but do not eradicate the organism in vitro. The cephalosporins appear to be relatively ineffective against *C. trachomatis*. Streptomycin, gentamicin, neomycin, kanamycin, vancomycin, ristocetin, spectinomycin, and nystatin are not effective at concentrations inhibitory for most bacteria and fungi. There does not appear to be much strain-to-strain variation in susceptibility to antibiotics, and no clinically significant antimicrobial resistance in chlamydiae has been described. Thus antimicrobial susceptibility testing is not needed in the routine management of patients with chlamydial infection, even recurrent infection.

## TREATMENT

Until the introduction of azithromycin, chlamydial infections could not be eradicated by single-dose or short-term antimicrobial regimens. In most uncomplicated infections in adults, 7 days of treatment with doxycycline or tetracycline have to be given for genital infections, but a 2-week course of therapy is recommended for complicated chlamydial infections (e.g.,PID, epididymitis) and at least a 3-week course forLGV. Failure of treatment of genital infections with a tetracycline usually indicates poor compliance or reinfection rather than the involvement of a drug-resistant strain.

Therapy for *C. trachomatis* urethritis is more efficacious than therapy for nonchlamydialNGU. *C. trachomatis* is eradicated from the urethra in nearly all cases by treatment with tetracycline hydrochloride (500 mg qid for 7 days) or doxycycline (100 mg

by mouth bid for 7 days).

Eradication of *C. trachomatis* from the cervix by tetracycline, doxycycline, and erythromycin, with doses and durations similar to those specified above for urethritis, has been demonstrated. Erythromycin base (500 mg qid for 10 to 14 days) is the regimen of choice for pregnant women with *C. trachomatis* infection. Amoxicillin (500 mg tid for 10 days) has also been used successfully in pregnant women. Tetracycline hydrochloride (500 mg qid) or doxycycline (100 mg bid) for 14 days produces clinical and microbiologic cure of epididymitis andPIDassociated with *C. trachomatis* infection, but in this situation a tetracycline should always be used together with a drug that is highly effective against gonorrhea.

Azithromycin is highly active against *C. trachomatis*, exhibits prolonged bioavailability, is concentrated intracellularly, and has offered the prospect of single-dose therapy for chlamydial infection for the first time. In comparative trials, a 1-g single dose of azithromycin has been as effective as 7 days of doxycycline for uncomplicated chlamydial infection. Azithromycin causes fewer adverse gastrointestinal reactions than do older macrolides such as erythromycin. The single-dose regimen of azithromycin has great appeal for the treatment of patients with uncomplicated chlamydial infection (especially those without symptoms and those with a likelihood of poor compliance) and of sexual partners of infected patients. These advantages must be weighed against the considerably greater cost of azithromycin than of doxycycline. Whenever possible, the single 1-g dose should be given as directly observed therapy. Although not approved by the U.S. Food and Drug Administration, the 1-g single-dose regimen of azithromycin appears to be safe and effective in the treatment of pregnant women.

Of the newer fluoroquinolones, ofloxacin (300 mg by mouth bid for 7 days) has been shown to be as effective as doxycycline for the treatment of chlamydial infection and appears to be safe and well tolerated. It cannot be used in pregnancy.

**Treatment of Sex Partners** The continued high prevalence of chlamydial infections in most parts of the United States is due primarily to the failure to diagnose -- and therefore treat -- patients with symptomatic or asymptomatic infection and their sex partners. *C. trachomatis* urethral or cervical infection has been well documented in a high proportion of the sex partners of patients withNGU, epididymitis, Reiter's syndrome, salpingitis, or endocervicitis. If possible, confirmatory laboratory tests for *Chlamydia* should be undertaken in these individuals, but even those without evidence of clinical disease who have recently been exposed to proven or possible chlamydial infection (e.g., NGU) should be offered therapy.

**Treatment of Neonates and Infants** In neonates with conjunctivitis or infants with pneumonia, erythromycin ethylsuccinate or estolate can be given orally in a dose of 50 mg/kg per day, preferably in four divided doses, for 2 weeks. Careful attention must be given to compliance with therapy -- a frequent problem. Relapses of eye infection are common following treatment with topical erythromycin or tetracycline ophthalmic ointment and may also occur after oral erythromycin therapy. Thus follow-up cultures should be performed after treatment. Both parents should be examined for *C. trachomatis* infection and, if diagnostic testing is not readily available, should be treated with doxycycline or azithromycin.

## PREVENTION

Efforts to develop a vaccine for chlamydial infection have not yet been successful. Early diagnosis and treatment shorten the duration of infectiousness of the carrier and therefore constitute primary prevention of chlamydial infection. By the early 1990s, one of the 10 regions of the United States (Region X, the Pacific Northwest) had formally undertaken a chlamydial control program involving widespread screening of women attending family planning clinics. Approximately 500,000 tests per year were conducted at 150 such clinics throughout the region in women meeting the criteria for high risk. Within 5 years, the prevalence of chlamydial infection had been reduced by>30% in this population. While other regions of the United States have now initiated similar programs, many family planning andSTDclinics still do not offer chlamydial testing. The availability of highly sensitive and specific diagnostic tests that can be done with urine specimens and of single-dose therapy makes it feasible to mount an effective chlamydial control program nationwide, with screening of high-risk persons both in traditional health care settings and in novel community- and school-based settings.

# TRACHOMA AND ADULT INCLUSION CONJUNCTIVITIS

## DEFINITION

Trachoma is a chronic conjunctivitis associated with infection by *C. trachomatis* serovar A, B, Ba, or C. It has been responsible for an estimated 20 million cases of blindness throughout the world and remains an important cause of preventable blindness. Inclusion conjunctivitis is an acute ocular infection caused by sexually transmitted *C. trachomatis* strains (usually serovars D through K) in adults exposed to infected genital secretions and in their newborn offspring.

## EPIDEMIOLOGY

Epidemiologically, two types of eye disease are caused by *C. trachomatis*. In trachoma-endemic areas where the classic eye disease is seen, transmission is from eye to eye via hands, flies, towels, and other fomites and usually involves serovar A, B, Ba, or C. In nonendemic areas, organisms of serovars D through K can be transmitted from the genital tract to the eye, usually causing only the inclusion conjunctivitis syndrome, occasionally with keratitis. Rarely, the eye disease acquired in this way progresses, with the development of pannus and scars similar to those seen in endemic trachoma. These cases may be referred to as paratrachoma to differentiate them epidemiologically from eye-to-eye-transmitted endemic trachoma.

The worldwide incidence and severity of trachoma have decreased dramatically during the past 35 years, mainly as a result of improving hygienic and economic conditions. Endemic trachoma is still the major cause of preventable blindness in northern Africa, sub-Saharan Africa, the Middle East, and parts of Asia. The endemic disease is transmitted primarily through close personal contact, particularly among young children in rural communities with limited water supplies. In endemic areas, trachoma is associated with repeated exposure and reinfection, but the infection can also become chronic and persistent. In the United States a mild form of endemic trachoma still occurs

in Mexican Americans as well as in immigrants from areas where trachoma is endemic. Acute relapse of old trachoma occasionally follows treatment with cortisone eye ointment or develops in very old persons who were exposed in their youth.

## CLINICAL MANIFESTATIONS

Both endemic trachoma and adult inclusion conjunctivitis present initially as a conjunctivitis characterized by small lymphoid follicles in the conjunctiva. In regions with hyperendemic classic blinding trachoma, the disease usually starts insidiously before the age of 2 years. Reinfection is common and probably contributes to the pathogenesis of trachoma. Studies usingPCRtechniques indicate that chlamydial DNA is often present in the ocular secretions of patients with trachoma, even in the absence of positive cultures. Thus persistent infection may be more common than was previously thought.

The cornea becomes involved, with inflammatory leukocytic infiltrations and superficial vascularization (pannus formation). As the inflammation continues, conjunctival scarring eventually distorts the eyelids, causing them to turn inward so that the inturned lashes constantly abrade the eyeball (trichiasis and entropion); eventually the corneal epithelium is abraded and may ulcerate, with subsequent corneal scarring and blindness. Destruction of the conjunctival goblet cells, lacrimal ducts, and lacrimal gland may produce a "dry-eye" syndrome, with resultant corneal opacity due to drying (xerosis) or secondary bacterial corneal ulcers.

Communities with blinding trachoma often experience seasonal epidemics of conjunctivitis due to *H. influenzae* that contribute to the intensity of the inflammatory process. In such areas the active infectious process usually resolves spontaneously in affected persons between 10 and 15 years of age, but the conjunctival scars continue to shrink, producing trichiasis and entropion and subsequent corneal scarring in adults. In areas with milder and less prevalent disease, the process may be much slower, with active disease continuing into adulthood; blindness is rare in these cases.

Eye infection with genital *C. trachomatis* strains in sexually active young adults presents as the acute onset of unilateral follicular conjunctivitis and preauricular lymphadenopathy similar to that seen in acute adenovirus or herpesvirus conjunctivitis. If untreated, the disease may persist for 6 weeks to 2 years. It is frequently associated with corneal inflammation in the form of discrete opacities ("infiltrates"), punctate epithelial erosions, and minor degrees of superficial corneal vascularization. Very rarely, conjunctival scarring and eyelid distortion occur, particularly in patients treated for many months with topical glucocorticoids. Recurrent eye infections develop most often in patients whose sexual consorts are not treated with antimicrobials.

## DIAGNOSIS

The clinical diagnosis of classic trachoma can be made if two of the following signs are present:

1. Lymphoid follicles on the upper tarsal conjunctiva

2. Typical conjunctival scarring

3. Vascular pannus

4. Limbal follicles or their sequelae, Herbert's pits

The clinical diagnosis of endemic trachoma should be confirmed by laboratory tests in children with more marked degrees of inflammation. Intracytoplasmic chlamydial inclusions are found in 10 to 60% of Giemsa-stained conjunctival smears in such populations, but isolation in cell cultures, newer antigen detection testing, or chlamydialPCR is more sensitive. Follicular conjunctivitis in adult Europeans or Americans living in trachomatous regions is rarely due to trachoma.

Sporadic cases of adult inclusion conjunctivitis must be differentiated from keratoconjunctivitis due to adenovirus orHSV and from bacterial conjunctivitis during the first 15 days after onset; later, they must be distinguished from other forms of chronic follicular conjunctivitis. Demonstration of chlamydiae by Giemsa- or immunofluorescent-stained smears, by isolation in cell cultures, or by newer nonculture tests constitutes definitive evidence of infection. Genital examination and tests for genital chlamydial infection are indicated. Serum antibody does not constitute evidence of chlamydial eye infection since many sexually active adults have acquired serum antibody from genital infection.

**TREATMENT**

Public health control programs for endemic trachoma have consisted of the mass application of tetracycline or erythromycin ointment to the eyes of all children in affected communities for 21 to 60 days or on an intermittent schedule. These programs also include surgical correction of inturned eyelids by a mobile surgical team that visits each locale. Single-dose azithromycin therapy is now being evaluated as an alternative method of mass antibiotic treatment for trachoma in young children and pregnant women.

Adult inclusion conjunctivitis responds well to treatment with full doses of systemic tetracycline or erythromycin for 3 weeks. Treatment of all sexual consorts of the patient simultaneously is also necessary to prevent ocular reinfection and to avoid genital disease due to chlamydial infection. Topical antibiotic treatment is not required for patients who receive systemic antibiotics.

**PREVENTION**

Efforts to develop a trachoma vaccine have not yet been successful. General hygienic measures associated with improved living standards are effective in the elimination of endemic trachoma. An adequate water supply for personal cleanliness may be a key factor. In some areas the reduction of numbers of flies in the household is important.

## PSITTACOSIS

**DEFINITION**

Psittacosis is primarily an infectious disease of birds and mammals that is caused by *C. psittaci*. Transmission of infection from birds to humans results in a febrile illness characterized by pneumonitis and systemic manifestations. Inapparent infections or mild influenza-like illnesses may also occur. The term *ornithosis* is sometimes applied to infections contracted from birds other than parrots or parakeets, but *psittacosis* is the preferred generic term for all forms of the disease.

## EPIDEMIOLOGY

Almost any avian species can harbor *C. psittaci*. Psittacine birds (parrots, parakeets, budgerigars) are most commonly infected, but human cases have been traced to contact with pigeons, ducks, turkeys, chickens, and many other birds. Psittacosis may be considered an occupational disease of pet-shop owners, poultry workers, pigeon fanciers, taxidermists, veterinarians, and zoo attendants. During the past 20 years, there has been an increase in incidence, with cases and outbreaks occurring primarily among employees of poultry-processing plants. It is suspected that many cases go undiagnosed and unreported. The disease appears to be especially common in England, where budgerigars are popular household pets and where restrictions on the importation of these birds have been eased.

The agent is present in nasal secretions, excreta, tissues, and feathers of infected birds. Although the disease can be fatal, infected birds frequently show only minor evidence of illness, such as ruffled feathers, lethargy, and anorexia. Asymptomatic avian carriers are common, and complete recovery may be followed by continued shedding of the organism for many months.

Psittacosis is almost always transmitted to humans by the respiratory route. On rare occasions the disease may be acquired from the bite of a pet bird. Prolonged contact is not essential for transmission of the disease; a few minutes spent in an environment previously occupied by an infected bird has resulted in human infection. In one outbreak, gardening rather than direct exposure to birds was associated with infection. A psittacosis-like agent has been transmitted among hospital personnel, with severe and sometimes fatal infections. There is evidence that these "human" strains are more virulent than avian organisms. There is no record of infection acquired by the ingestion of poultry products.

## PATHOGENESIS

The psittacosis agent gains entrance to the body through the upper part of the respiratory tract, spreads via the bloodstream, and eventually localizes in the pulmonary alveoli and in the reticuloendothelial cells of the spleen and liver. Invasion of the lung probably takes place by way of the bloodstream rather than by direct extension from the upper air passages. A lymphocytic inflammatory response occurs on both the interstitial and the respiratory surfaces of the alveoli as well as in the perivascular spaces. The alveolar walls and interstitial tissues of the lung are thickened, edematous, necrotic, and occasionally hemorrhagic. Histologic examination of the affected areas reveals alveolar spaces filled with fluid, erythrocytes, and lymphocytes. The picture is not pathognomonic of psittacosis unless macrophages containing characteristic cytoplasmic inclusion bodies (Levinthal-Coles-Lillie bodies) can be identified. The respiratory

epithelium of the bronchi and bronchioles usually remains intact.

## CLINICAL MANIFESTATIONS

The clinical manifestations and course of psittacosis are extremely variable. After an incubation period of 7 to 14 days or longer, the disease may start abruptly with shaking chills and fever, with temperatures ranging as high as 40.5°C (105°F); however, the onset is often gradual, with fever increasing over a 3- to 4-day period. Headache is almost always a prominent symptom; it is usually diffuse and excruciating and is often the patient's chief complaint.

Many patients present with a dry hacking cough that is usually nonproductive, but small amounts of mucoid or bloody sputum may be raised as the disease progresses. Cough may begin early in the course of the disease or as late as 5 days after the onset of fever. Chest pain, pleurisy with effusion, or a friction rub may all occur but are rare. Pericarditis and myocarditis have been reported. Most patients have a normal or slightly increased respiratory rate; marked dyspnea with cyanosis occurs only in severe psittacosis with extensive pulmonary involvement. In psittacosis, as in mycoplasmal pneumonias, the physical signs of pneumonitis tend to be less prominent than symptoms and x-ray findings would suggest. The initial examination may reveal fine sibilant rales, or clinical evidence of pneumonia may be completely lacking. Rales usually become audible and more numerous as the illness progresses. Signs of frank pulmonary consolidation are usually absent. Symptoms of upper respiratory tract infection are not prominent, although mild sore throat, pharyngitis, and cervical adenopathy are often documented; on occasion, the last may be the only manifestation of illness. Epistaxis is encountered early in the course of nearly one-fourth of cases. Photophobia is also a common complaint.

Patients often report generalized myalgia, and spasm and stiffness of the muscles of the back and neck may lead to an erroneous diagnosis of meningitis. Lethargy, mental depression, agitation, insomnia, and disorientation have been prominent features of the illness in some epidemics but not in others; delirium and stupor develop near the end of the first week in severe cases. Occasional patients are comatose when first seen, and the diagnosis of psittacosis may be elusive in these cases. Gastrointestinal manifestations such as abdominal pain, nausea, vomiting, or diarrhea are noted in some cases; constipation and abdominal distention sometimes occur as late complications. Icterus, the result of severe hepatic involvement, is a rare and ominous finding. A faint macular rash (Horder's spots) resembling the rose spots of typhoid fever has been described.

Patients without cough or other clinical evidence of respiratory involvement present with fever of unknown origin (Chap. 125). The pulse rate is slow in relation to the fever. When splenomegaly is noted in a patient with acute pneumonitis, psittacosis should be considered; the reported incidence of splenomegaly in this disease ranges from 10 to 70%. Nontender hepatic enlargement also occurs, but jaundice is rare. Thrombophlebitis is not unusual during convalescence; indeed, pulmonary infarction is sometimes a late complication and may be fatal.

In untreated cases of psittacosis, sustained or mildly remittent fever persists for 10 days

to 3 weeks or occasionally for as long as 3 months. Over this period, the respiratory manifestations gradually abate. Psittacosis contracted from parrots or parakeets is more likely to be a severe, prolonged illness than infection acquired from pigeons or barnyard fowl. Relapses occur but are rare. Occasional patients develop endocarditis, and *C. psittaci* infection should be considered in cases of culture-negative endocarditis. Secondary bacterial infections are uncommon. Immunity to reinfection is probably permanent.

## LABORATORY FINDINGS

The chest x-ray in psittacosis is nonspecific and may show pneumonic lesions that are usually patchy in appearance but can be hazy, diffuse, homogeneous, lobar, atelectatic, wedge-shaped, nodular, or miliary. The white blood cell count is normal or moderately decreased in the acute phase of the disease but may rise in convalescence. The erythrocyte sedimentation rate frequently is not elevated. Transient proteinuria is common. The cerebrospinal fluid sometimes contains a few mononuclear cells but is otherwise normal. Despite hepatomegaly, the results of liver function tests are generally normal or mildly elevated.

The diagnosis can be confirmed only by isolation of the causative microorganism or by serologic studies. The agent is present in the blood during the acute phase of the disease and in the bronchial secretions for weeks or sometimes years after infection, but it is difficult to isolate. Further, the organism is hazardous to work with in the laboratory, and most clinical laboratories do not offer culture for *C. psittaci*. Thus psittacosis is most readily diagnosed by the demonstration of a rising titer of complement fixation antibody in the serum of a patient with a compatible clinical syndrome. Both an acute-phase and a convalescent-phase specimen should always be tested. *C. trachomatis*, *C. psittaci*, and *C. pneumoniae* all share a genus-specific "group" antigen, which is the basis of the complement fixation test. Thus acute infections with *C. trachomatis* or *C. pneumoniae* can also produce titer rises in this test. However, these three species have different major outer-membrane proteins that are the principal antigens in themicro-IFtest. If there is doubt as to the interpretation of the complement fixation test, the micro-IF test can be used to differentiate among these antigens. The prompt initiation of treatment with tetracycline has been shown to delay an antibody rise in convalescence for several weeks or months.

## DIFFERENTIAL DIAGNOSIS

A history of exposure to birds may be the only clinical basis for differentiating psittacosis from a variety of infectious and noninfectious febrile disorders. The list of pulmonary diseases that may be confused with psittacosis includes *Mycoplasma* pneumonia, *C. pneumoniae* pneumonia, legionellosis, viral pneumonia, Q fever, coccidioidomycosis, tuberculosis, enterovirus infection, carcinoma of the lung with bronchial obstruction, and common bacterial pneumonias. In the early stages, before pneumonitis appears, psittacosis may be mistaken for influenza, typhoid fever, miliary tuberculosis, or infectious mononucleosis.

## TREATMENT

The tetracyclines are consistently effective in the treatment of psittacosis. Defervescence and alleviation of symptoms usually take place within 24 to 48 h after the institution of therapy with 2 g daily in four divided doses. To avoid relapse, treatment should probably be continued for at least 7 to 14 days after defervescence. In severe cases, hospitalization and pulmonary intensive care may be indicated. Sulfonamides are not active against *C. psittaci*. Erythromycin can be used in patients allergic to or intolerant of tetracyclines.

## *C. PNEUMONIAE* INFECTIONS

A third chlamydial species that causes disease in humans, *C. pneumoniae*, has been described in the past two decades. *C. pneumoniae* can be distinguished from the other two species on the basis of DNA hybridization and elementary body morphology. Although *C. pneumoniae* can be grown in a variety of cell cultures, it is considerably more difficult to culture than other chlamydiae, especially from clinical specimens. HL cells appear to be the most effective cell line for isolation of *C. pneumoniae*.

Knowledge of the epidemiology of *C. pneumoniae* infections has been derived primarily from serologic studies. Infections begin to occur in late childhood, achieve peak incidence in young adults, but continue throughout adult life. Seroprevalence in the many adult populations that have been tested throughout the world exceeds 40% -- a figure suggesting that *C. pneumoniae* infections are ubiquitous. Secondary episodes (reinfections) appear to occur commonly in older adults throughout life. *C. pneumoniae* also produces epidemics of pneumonia and respiratory illness, especially in close residential quarters such as military barracks. The incidence of infections outside of epidemics remains poorly defined. Transmission appears to be from person to person, probably primarily in schools and family units.

Little is known about the pathogenesis of *C. pneumoniae* infection. The infection begins in the upper respiratory tract and in many persons is a long-lived asymptomatic condition of the upper respiratory mucosal surfaces. However, in at least some individuals, the organism is transported to distant sites -- perhaps within macrophages -- since evidence exists for replication within arteries and synovial membranes of joints. A *C. pneumoniae* outer-membrane protein may induce host immune responses whose cross-reaction with human proteins results in an autoimmune reaction.

The clinical spectrum of *C. pneumoniae* infection includes acute pharyngitis, sinusitis, bronchitis, and pneumonitis, primarily in young adults. The clinical manifestations of primary infection appear to be more severe and prolonged than those of reinfection. The pneumonitis resembles that of *M. pneumoniae* pneumonia in that leukocytosis is frequently lacking and patients often have prominent antecedent upper respiratory tract symptoms, fever, nonproductive cough, a mild to moderate degree of illness, minimal findings on chest auscultation, and small segmental infiltrates on chest x-ray. In elderly patients, pneumonia due to *C. pneumoniae* can be especially severe and may necessitate hospitalization and respiratory support.

Epidemiologic studies have demonstrated an association between serologic evidence of *C. pneumoniae* infection and atherosclerotic disease of the coronary and other arteries. In addition, *C. pneumoniae* has been identified in atherosclerotic plaques by electron

microscopy, DNA hybridization, and immunocytochemistry. Recently, the organism has been recovered in culture from atheromatous plaque -- a result indicating the presence of viable replicating bacteria in vessels. Evidence from animal models supports the hypothesis that *C. pneumoniae* infection of the upper respiratory tract is followed by recovery of the organism from atheromatous lesions in the aorta and that the infection accelerates the process of atherosclerosis, especially in hypercholesterolemic animals. Antimicrobial treatment of the infected animals reverses the increased risk of atherosclerosis. In humans, two small trials in patients with unstable angina or recent myocardial infarction also suggested that antibiotics reduce subsequent untoward cardiac events. Larger trials have been initiated to determine more definitively whether antibiotics affect the risk of atherosclerosis.

Diagnosis of *C. pneumoniae* infection is currently difficult because cell culture techniques are not available for routine clinical use and nonculture tests using antigen detection methods or DNA probes have not been developed for commercial use. Acute- and convalescent-phase sera can be tested for chlamydial complement fixation antibody to make a retrospective diagnosis. However, this test does not distinguish *C. pneumoniae* infection from infection due to *C. trachomatis* or *C. psittaci*. Although controlled treatment trials have not been conducted, *C. pneumoniae* is inhibited in vitro by erythromycin and tetracycline. Recommended therapy consists of 2 g per day of either agent for 10 to 14 days. Other macrolides, such as azithromycin, and some fluoroquinolones, such as levofloxacin, also appear to be effective.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## SECTION 11 -VIRAL DISEASES

# 180. MEDICAL VIROLOGY - *Fred Wang*, *Elliott Kieff*

## DEFINING A VIRUS

Viruses consist of a nucleic acid surrounded by one or more proteins. Some viruses also have an outer-membrane envelope. Viruses differ from other replicating organisms in that they do not have ribosomes or enzymes for high-energy phosphate generation or for protein, carbohydrate, or lipid metabolism. Viruses are obligate intracellular parasites -- that is, they require cells in order to replicate. Typically, viral nucleic acids encode proteins necessary for replicating and packaging the nucleic acids into new viral particles.

Viruses differ from viroids, prions, and virusoids. *Virusoids* are nucleic acids that depend on helper viruses to package the nucleic acids into virus-like particles. *Viroids* are simply molecules of naked, cyclical, mostly double-stranded, small RNAs and appear to be restricted to plants, in which they spread from cell to cell and are replicated by cellular RNA polymerase II. *Prions* (Chap. 375) are protein molecules that can spread from cell to cell and effect changes in the structure of their normal counterparts (cellular proteins). Prions have been implicated in neurodegenerative conditions such as Creutzfeldt-Jakob disease, kuru, and Gerstmann-Straussler disease. Prions have also been implicated in neurodegeneration associated with human infection with bovine spongiform encephalopathy ("mad cow disease").

## VIRAL STRUCTURE

Viruses have from a few to 200 genes. These genes may be embodied in a single-strand or double-strand DNA genome or in a single-strand sense, a single-strand or segmented antisense, or a double-strand segmented RNA genome. Sense-strand RNA genomes can be translated directly into protein. Sense and antisense genomes are also referred to as positive-strand and negative-strand genomes, respectively. The viral nucleic acid is usually associated with one or more virus-encoded nucleoproteins in the core of the viral particle. The viral nucleic acid is almost always enclosed in a protein shell called a *capsid*. Because of the limited genetic complexity of viruses, their capsids are usually composed of multimers of identical capsomers. Capsomers are in turn composed of one or a few proteins. Capsids have icosahedral or helical symmetry. Icosahedral structures approximate spheres but have two-, three-, and fivefold axes of symmetry, while helical structures have only a twofold axis of symmetry. The entire structural unit of nucleic acid, nucleoprotein(s), and capsid is called a *nucleocapsid*. Many human viruses have a simple nucleocapsid structure. For these viruses, the outer surface of the capsid mediates contact with uninfected cells. Other viruses are more complex and have an outer envelope that is derived from membranes of the infected cell. The piece of infected cell membrane that becomes the viral envelope has usually been modified during infection by the insertion of virus-encoded glycoproteins. These glycoproteins usually mediate contact of enveloped viruses with uninfected cells. Enveloped viruses frequently have matrix or tegument proteins that fill the space between the nucleocapsid and the envelope. In general, enveloped viruses are sensitive to solvents and nonionic detergents that can disrupt the envelope, while viruses that

consist only of nucleocapsids are usually more resistant. The schematic diagram of a large and complex herpesvirus shown in Fig. 180-1 illustrates the components of a complicated DNA virus. Prototypical pathogenic human viruses are listed in Table 180-1. The relative sizes and structures of typical pathogenic human viruses are shown in Fig. 180-2.

## TAXONOMY OF PATHOGENIC HUMAN VIRUSES

As is apparent from Table 180-1 and Fig. 180-2, the classification of viruses into orders and families is based on nucleic acid composition, nucleocapsid size and symmetry, and envelopment status. Viruses of a single family have similar types of genomes and are morphologically similar in electron micrographs. Further subclassification into genus is dependent on similarities in epidemiology and biologic effects and on the degree of colinear nucleic acid sequence homology. In general, each human virus has a common name related to its pathologic effects or the circumstances of its discovery and a formal species name assigned by the International Committee on Taxonomy of Viruses. The latter designation consists of the name of the host followed by the family or genus of the virus and a number. This dual terminology has created a confusing situation in which viruses are referred to and referenced by either name -- e.g., varicella-zoster virus (VZV) or human herpesvirus (HHV) 3.

## VIRAL INFECTION IN VITRO

### STAGES OF INFECTION

At the cellular level, viral infection proceeds in stages.

**Viral Interactions at the Cell Surface** First, virus adsorbs to a receptor on the cell surface. Adsorption is the consequence of a molecular interaction of a viral surface protein with a molecule on the cell's plasma membrane. For example, a poliovirus capsid protein binds to a cell plasma-membrane protein of the immunoglobulin superfamily type; a rhinovirus capsid protein binds to intracellular adhesion molecule 1; an echovirus capsid protein binds to an integrin; the influenza A virus envelope hemagglutinin protein binds to sialic acid; the HIV envelope glycoprotein binds to CD4 and then engages one of several chemokine receptors that function as coreceptors for the virus; the herpes simplex virus (HSV) envelope glycoproteins bind to heparan sulfate on cell surfaces and then engage one of several immunoglobulin superfamily or tumor necrosis factor (TNF) receptors; and an Epstein-Barr virus (EBV) glycoprotein binds to the B lymphocyte complement receptor CD21. Adsorption characteristically proceeds almost as well at 4°C as at 37°C, and adsorbed virus can still be neutralized by antibody. Adsorption frequently initiates changes in virion surface proteins that result in destabilization and preparation for the next stage of entry into the cell.

After adsorption, viruses penetrate through or fuse with the cell membrane, lose their sensitivity to neutralizing antibody, and become uncoated as they enter the cytoplasm. For all viruses, penetration and uncoating result in viral nucleocapsid or nucleoprotein entry into the cytoplasm. Penetration and uncoating as well as subsequent steps in viral replication depend on the cell's energy metabolism and on biochemical changes in the cell's plasma membrane and cytoskeleton. Therefore, penetration proceeds slowly at

temperatures<37°C. Viruses use various strategies to penetrate and enter cells. Interaction of the viral surface protein with a cellular receptor can induce changes in viral glycoproteins or capsid proteins and in cell-surface proteins, with consequent penetration. The interaction of multiple protein molecules on the viral surface with multiple molecules on the cell-surface receptor may induce receptor aggregation at the site of viral adsorption. Receptor aggregation can trigger signaling events within the cytoplasm and changes in the plasma membrane. The cell frequently misperceives that the receptor has encountered its "normal ligand," and the aggregated receptor is internalized with the attached virus through an endocytic process that involves clathrin-coated pits. Endocytosis is important in the entry of viruses as diverse as picornaviruses, influenza viruses, HIV, adenoviruses, and herpesviruses. In many cases, entry of the virus into the cytoplasm depends on acidification of the viral endosome.

One of the best-studied examples of the effect of low pH on viral penetration is influenza virus. Influenza hemagglutinin mediates adsorption, receptor aggregation, and endocytosis. In low-pH endosomes, changes in the conformation of the hemagglutinin expose amphipathic domains that interact chemically with the cell membrane and initiate fusion of the viral and cellular membranes. Data indicate that the HIV envelope glycoprotein undergoes similar conformational changes after interaction with CD4 and chemokine receptors. For influenza virus, the M2 membrane protein also plays a key role in the uncoating of the viral envelope by providing an ion channel in the envelope. Fusion of viral and cell membranes results in the mixture of viral envelope lipids and proteins with cell membrane lipids and proteins and the penetration of the influenza nucleocapsid into the cytoplasm. Little is known about the details of the fusion processes or the subsequent biochemical interactions. With more complex viruses, such as herpesviruses, different glycoproteins interact with different receptors on different cell types or on different surfaces of polarized epithelial cells. Viral glycoproteins other than the protein that mediates initial adsorption may be critical in mediating envelope fusion with cell membranes.

**Viral Gene Expression and Replication** After uncoating and release of viral nucleoprotein into the cytoplasm, the viral genome is transported to a site for expression and replication. In order to produce infectious progeny, viruses must (1) replicate their nucleic acid, (2) produce structural proteins, and (3) assemble the nucleic acid and proteins into progeny virions. Different viruses use different strategies and gene repertoires to accomplish these goals. DNA viruses (except for poxviruses) replicate their nucleic acid and assemble into nucleocapsid complexes in the cell nucleus. RNA viruses (except for influenza viruses) transcribe and replicate their nucleic acid and assemble entirely in the cytoplasm. Thus, the replication strategies of DNA and RNA viruses are presented separately below. Positive-strand and negative-strand RNA viruses are discussed separately. Medically important viruses of each group are used for illustrative purposes.

*Positive-Strand RNA Viruses* Medically important positive-strand RNA viruses include picornaviruses, flaviviruses, togaviruses, and caliciviruses. Genomic RNA from positive-strand RNA viruses is released into the cytoplasm without associated enzymes. Cell ribosomes recognize and associate with an internal ribosome entry sequence in the viral genomic RNA and translate a polyprotein that is a fusion of many or all of the viral

proteins. The viral RNA polymerase and other viral proteins are cleaved from the polyprotein by protease components of the polyprotein. Antigenomic RNA is then transcribed from the genomic RNA template. Positive-strand genomes and mRNAs are next transcribed from the antigenomic RNA by the viral RNA polymerase. Positive-strand genomic RNA is encapsidated in the cytoplasm.

*Negative-Strand RNA Viruses* Medically important negative-strand RNA viruses include rhabdoviruses, filoviruses, paramyxoviruses, and bunyaviruses. Negative-strand RNA virus genomes are released into the cytoplasm with an associated RNA polymerase and one or more accessory proteins. Except for influenza viruses, negative-strand RNA viruses replicate entirely in the cytoplasm. The viral RNA polymerase transcribes messenger RNAs (mRNAs) as well as full-length antigenomic RNA, which is the template for replication of genomic RNA. The mRNAs encode for RNA polymerase and accessory factors as well as for viral structural proteins. Influenza virus is an unusual negative-strand RNA virus that transcribes its mRNAs and antigenomic RNAs in the cell's nucleus. The influenza genome RNA snatches cellular mRNA cap sequences to enhance translation of viral mRNAs and uses cell splicing machinery to encode additional viral mRNAs. All negative-strand RNA viruses, including influenza viruses, assemble in the cytoplasm.

*Double-Strand Segmented RNA Viruses* These viruses, which are taxonomically grouped in the reovirus family, have 10 to 12 RNA segments that make up their genome. The medically important viruses in this group are rotaviruses and Colorado tick fever virus. Reovirus virions include an RNA polymerase complex. Reoviruses replicate and assemble in the cytoplasm.

*DNA Viruses* Medically important DNA viruses include parvoviruses, papovaviruses, human papillomaviruses (HPVs), adenoviruses, herpesviruses, and poxviruses. Other than poxviruses, most DNA viruses must get to the cell's nucleus for DNA transcription by cellular RNA polymerase II. For example, after receptor binding and fusion, herpesvirus nucleocapsids are released into the cytoplasm along with tegument proteins. The complex is then transported along microtubules to nuclear pores, and the DNA is released into the nucleus.

Transcriptional regulation and mRNA processing for nuclear DNA viruses depend on both viral and cellular proteins. For herpesviruses, the viral tegument protein can activate transcription of viral immediate-early genes, a class of genes expressed immediately after infection. Transcription of immediate-early genes requires the virus tegument protein and preexisting cellular transcription factors. One of the key preexisting cellular factors forHSV-1 immediate-early gene transcription is docked in the cytoplasm in neurons; this fact may explain why HSV-1 goes into a latent state in neurons.

Transcription is often regulated into an organized cascade of viral gene expression. Herpesvirus immediate-early genes turn on the promoters for early genes. Other DNA viruses are not as dependent on transactivators encoded from the viral genome for early-gene transcription. Most early genes encode proteins that are necessary for viral DNA synthesis and for the turn-on of late-gene transcription. Late genes encode mostly viral structural proteins or viral proteins necessary for the assembly and egress of the

virus from the infected cell. Late-gene transcription is continuously dependent on DNA replication. Therefore, inhibitors of DNA replication also stop late-gene transcription.

Each DNA virus family uses unique mechanisms for replicating its DNA. Herpesvirus DNAs are linear in the virion but circularize in the infected cell. In lytic virus infection, circular herpesvirus genomes are replicated into linear concatemers through a "rolling-circle" mechanism. Herpesviruses encode a DNA polymerase and at least six other viral proteins necessary for viral DNA replication; these viruses also encode several enzymes that increase the pool of precursor deoxynucleotide triphosphates. Adenovirus genomes are linear in the virion and are replicated into complementary linear copies by a virus-encoded DNA polymerase and an initiator protein complex. The double-strand circular papovavirus genomes are replicated into progeny circular DNA molecules by cellular DNA replication enzymes. Two viral early proteins contribute to viral DNA replication and to the persistence of papovavirus DNA in latently infected cells. Other early papovavirus proteins stimulate cells to remain in cycle, thus facilitating viral DNA replication. Occasionally,HPVsintegrate into the host chromosome; overexpression of viral early proteins and excessive stimulation of cellular growth result. Sometimes the consequence is the development of malignancies such as cervical cancer (see "Persistent Viral Infections and Cancer," below). Parvoviruses are the smallest DNA viruses: their genomes are half the size of the papovavirus genomes and include only two genes. Parvoviruses have negative single-strand DNA genomes. The replication of autonomous parvoviruses, such as B19, depends on cellular DNA replication and requires the virus-encoded Rep protein. Other parvoviruses, such as adeno-associated virus (AAV), are not autonomous and require helper viruses of the adenovirus or herpesvirus family for their replication. AAV has been touted as a potentially safe human gene vector because its Rep protein causes its integration at a single chromosomal site.

Poxviruses are the largest DNA viruses and are unique among these viruses in replicating and assembling in the cytoplasm. Poxviruses encode transcription factors and an RNA polymerase as well as enzymes for RNA capping and polyadenylation and for DNA synthesis. Poxvirus DNA also has a unique structure. The two strands of the double-strand linear DNA are covalently linked at the ends so that the genome is also a covalently closed single-strand circle. In addition, there are inverted repeats at the ends of the DNA. During DNA replication, the genome is cleaved within the terminal inverted repeat, and the inverted repeats self-prime complementary-strand synthesis by the virus-encoded DNA polymerase. Like herpesviruses, poxviruses encode several enzymes that increase deoxynucleotide triphosphate precursor levels and thus facilitate viral DNA synthesis.

*Viruses with Both RNA and DNA Genomes* Retroviruses, lentiviruses, and hepatitis B virus (HBV) are not purely RNA or DNA viruses.

Retroviruses and lentiviruses are enveloped RNA viruses with two identical sense-strand genomes and associated reverse transcriptase and integrase enzymes. Retroviruses and lentiviruses differ from all other viruses in that they reverse-transcribe themselves into partially duplicated double-strand DNA copies and then routinely integrate into the host genome as part of their replication strategy. Cellular RNA polymerase II and transcription factors regulate transcription from the integrated

provirus genome. Some retroviruses also encode for regulators of transcription and RNA processing, such as Tax and Rex in the human T-lymphotropic virus (HTLV) types I and II and Tat and Rev in HIV-1 and HIV-2. Full-length proviral transcripts are made from a promoter in the viral terminal repeat and serve as both genomic RNAs that will be packaged in the nucleocapsids and mRNAs that encode for the viral Gag protein, polymerase/integrase protein, and envelope glycoprotein. The Gag protein includes a protease that cleaves it into several components, including a viral matrix protein that coats the viral RNA. Viral RNA polymerase/integrase, matrix protein, and cellular tRNA are key components of the viral nucleocapsid. The HIV Gag protease has been an important target for inhibition of HIV replication. Remnants of simple retroviral DNA in the human genome suggest that there may be replication-competent simple human retroviruses, but little other evidence supports the existence of these viruses.

HBVreplication is unique because the virus encodes and packages in the virion a reverse transcriptase and genomic RNA, which is then copied into an incomplete double-strand circular DNA genome before the virion matures in the infected cell. On entry into the cytoplasm, the virion reverse transcriptase/DNA polymerase completes DNA synthesis, and the covalently closed circular genome resides in the nucleus. Viral mRNAs are transcribed from the closed circular viral episome by cellular RNA polymerase II. A capped and polyadenylated, full-genome-length, terminally redundant transcript is packaged into virus core particles in the cytoplasm of infected cells. This RNA associates with the viral reverse transcriptase. The reverse transcriptase converts the full-length, terminally redundant, core-particle, encapsidated RNA genome into partially double-strand DNA. HBV is believed to mature by budding through the cell's plasma membrane, which has been modified by the insertion of viral surface antigen protein.

**Viral Assembly and Egress** For most viruses, nucleic acid and structural protein synthesis are accompanied by the assembly of protein and nucleic acid complexes. The assembly and egress of mature infectious virus mark the end of the eclipse phase of infection, during which infectious virus cannot be recovered from the infected cell. Nucleic acids from RNA viruses and poxviruses assemble into nucleocapsids in the cytoplasm. For all DNA viruses except poxviruses, viral DNA assembles into nucleocapsids in the nucleus. In general, the capsid proteins of viruses with icosahedral nucleocapsids can self-assemble into densely packed and highly ordered capsid structures. Herpesviruses require an assemblin protein as a scaffold for capsid assembly. Viral nucleic acid then spools into the assembled capsid. For herpesviruses, a full unit of the viral DNA genome is packaged into the capsid, and a capsid-associated nuclease cleaves the viral DNA at both ends. In the case of viruses with helical nucleocapsids, the protein component appears to assemble around the nucleic acid, which contributes to capsid organization.

Viruses must egress from the infected cell and not bind back to its plasma membrane. In many cases, enveloped viruses simply egress and acquire their envelope by budding through the cell's plasma membrane. Excess viral membrane glycoproteins are synthesized to saturate cell receptors and facilitate viral egress. Some viruses encode membrane proteins with enzymatic activity for receptor destruction. Influenza virus, for example, encodes a glycoprotein with neuraminidase activity, which destroys sialic acid on the infected cell's plasma membrane. Herpesvirus nucleocapsids acquire their initial

envelope by assembling in the nucleus and then budding through the nuclear membrane into the endoplasmic reticular space. The enveloped herpesvirus is then released from the cell either by maturation in cytoplasmic vesicles, which fuse with the plasma membrane and release the virus by exocytosis, or by "de-envelopment" into the cytoplasm and "re-envelopment" at the plasma membrane. In most instances, nonenveloped viruses appear to depend on the death and dissolution of the infected cell for their release.

## FIDELITY OF VIRAL REPLICATION

Cells grow by doubling their genome and dividing, whereas viruses typically make large quantities of viral nucleic acid and structural proteins, and thousands of progeny may be produced from a single infected cell. Many particles partially assemble and never mature into virions. Many mature-appearing virions are imperfect and have only incomplete or nonfunctional genomes. Despite the inefficiency of assembly, a typical virus-infected cell releases 10 to 1000 infectious progeny. Some of these progeny may contain genomes that differ from those of the virus that infected the cell. Smaller, "defective" virus genomes have been noted with the replication of many RNA and DNA viruses. Virions with defective genomes can be produced in large numbers through packaging of incompletely synthesized nucleic acid. Adenovirus packaging is notoriously inefficient, and a high particle-to-infectious virus ratio may limit the amount of recombinant adenovirus that can be administered for gene therapy. Mutant viral genomes are also produced and can be of medical significance. In general, viral nucleic acid replication is more error-prone than cellular nucleic acid replication. RNA polymerases and reverse transcriptases are intrinsically more error-prone than DNA polymerases. Mutant viruses can be virulent and may preferentially cause disease through evasion of the host immune response or through resistance to antiviral drugs. Persistent hepatitis C virus (HCV) infection appears to be due to genome mutation and persistent immune escape. Changes in viral nucleic acid can also take place through infection by and recombination or reassortment between two related viruses in a single cell. While this occurrence is highly unusual, the changes could be substantial and could significantly alter virulence or epidemiology. Reassortment of an avian or mammalian influenza A hemagglutinin gene into a human influenza background is believed to play a role in the emergence of new epidemic influenza A strains.

## VIRAL GENES NOT REQUIRED FOR VIRAL REPLICATION

Viruses frequently have genes encoding proteins that are not directly involved in replication or packaging of the viral nucleic acid, in virion assembly, or in regulation of the transcription of viral genes involved in those processes. Most of these proteins fall into four classes: (1) proteins that directly or indirectly alter cell growth; (2) proteins that inhibit cellular DNA, RNA, or protein synthesis so that viral mRNA can be efficiently transcribed or translated; (3) proteins that promote the cell's survival or inhibit apoptosis so that progeny virus can mature and escape from the infected cell; and (4) proteins that downregulate host inflammatory or immune responses so that virus infection can proceed in an infected person to the maximum extent consistent with virus survival and efficient transmission to a new host. More complex viruses of the poxvirus or herpesvirus family encode many proteins that serve these functions. Some of these viral proteins have motifs similar to those of cell proteins, while others are quite novel.

Virology has increasingly focused on these more sophisticated strategies evolved by viruses to permit the establishment of long-term infection in humans and other animals. These strategies often provide unique insights into the control of cell growth, cell survival, macromolecular synthesis, proteolytic processing, immune or inflammatory suppression, immune resistance, cytokine mimicry, or cytokine blockade.

## HOST RANGE

The concept of host range was originally based on the cell types in which a virus replicated in tissue culture. For the most part, the host range is limited by specific cell-surface proteins required for viral adsorption or penetration. Another common basis for host-range limitation is transcription from viral promoters. Most DNA viruses depend not only on cellular RNA polymerase II and the basal components of the cellular transcription complex but also on activated components and transcriptional accessory factors, both of which differ among differentiated tissues, among cells at various phases of the cell cycle, and between resting and cycling cells.

The concept of host range for virus infection in humans includes these factors and others since (1) most viruses infect more than one cell type in vivo and (2) the virus life cycle and extent of viral replication can be affected by the differentiation and activated state of a given cell type. This point is particularly relevant for human papovavirus, herpesvirus, and lentivirus infections, in which vigorous replication during initial infection may be followed by quiescent or latent infection -- a situation that allows the virus to persist.

## VIRAL CYTOPATHIC EFFECTS AND INHIBITORS OF APOPTOSIS

The replication of almost all viruses has adverse effects on the infected cell, inhibiting cellular synthesis of DNA, RNA, or proteins. This inhibitory effect probably stems from the viruses' need to prevent or limit nonspecific, innate host resistance factors, including interferon (IFN). Most commonly, viruses specifically inhibit host protein synthesis by attacking a component of the translational initiation complex -- frequently, a component that is not required for efficient translation of viral RNAs. Poliovirus protease 2A, for example, cleaves a cellular component of the complex that ordinarily facilitates translation of cell mRNAs by interacting with their 5¢ cap structure. Poliovirus RNA is efficiently translated without a 5¢ cap since it has an internal ribosome entry sequence. Influenza virus inhibits the processing of mRNA by snatching 5¢ cap structures from nascent cellular RNAs and using them as primers in the synthesis of viral mRNA.HSV has a virion tegument protein that inhibits cellular mRNA translation.

Apoptosis is the expected consequence of virus-induced inhibition of cellular macromolecular synthesis and viral nucleic acid replication. While the induction of apoptosis may be important for the release of some viruses (particularly nonenveloped viruses), many viruses have acquired genes or parts of genes that enable them to forestall infected-cell apoptosis. This delay may be advantageous in allowing the completion of viral replication. Adenoviruses and herpesviruses encode analogues of the cellular Bc12 protein, which blocks mitochondrial enhancement of proapoptotic stimuli. Poxviruses and some herpesviruses encode caspase inhibitors. Many viruses, includingHPVs and adenoviruses, encode proteins that inhibit p53 or its downstream

proapoptotic effects.

## VIRAL INFECTION IN VIVO

The capsid and envelope of a virus protect its genome and permit its transmission from cell to cell and to prospective hosts. Most common viral infections are spread by aerosolized particles, by ingestion of contaminated water or food, or by direct contact. In all these situations, infection begins on an epithelial or mucosal surface and spreads along it or from it to deeper tissues. Infection may then spread through the body via the bloodstream, lymphatics, or neural circuits. Parenteral inoculation also serves to transmit some viral infections among humans or from animals (including insects) to humans.

### PRIMARY INFECTION

The first (primary) episode of viral infection usually lasts from several days to several weeks. During this period, the concentration of virus at sites of infection rises and then falls, usually to unmeasurable levels. The rate at which the intensity of viral infection rises and falls at a given site depends on the accessibility of that organ or tissue to both the virus and systemic immune effectors, the intrinsic ability of the virus to replicate at that site, and endogenous nonspecific and specific resistance. Typically, infections with enterovirus, mumps virus, measles virus, rubella virus, rotavirus, influenza virus, adenovirus,HSV, andVZV are cleared from almost all sites within 3 to 4 weeks. Some of these viruses are especially proficient in altering or evading the innate and acquired immune responses; thus primary infection with these viruses can last for several months. Characteristically extending beyond several weeks are primary infections due toHBV,HCV, hepatitis D virus (HDV),EBV, cytomegalovirus (CMV), HIV,HPV, and molluscum contagiosum virus. For some of these viruses (e.g., HPV, HBV, HCV, HDV, and molluscum contagiosum virus), the primary phase of infection is almost indistinguishable from the persistent phase.

Disease manifestations usually arise as a consequence of viral replication at a specific site but do not necessarily correlate with levels of replication at that site. For example, the clinical manifestations of limited infection with poliovirus, enterovirus, rabies virus, measles virus, mumps virus, orHSV in neural cells are severe relative to the level of viral replication at mucosal surfaces. Similarly, significant morbidity may accompany in utero fetal infection with rubella virus orCMV.

Primary infections are cleared by specific and nonspecific immune responses. Thereafter, an immunocompetent host is usually immune to the disease manifestations of reinfection by the same virus. Immunity may not prevent transient surface colonization on reexposure, or even persistent colonization.

### PERSISTENT AND LATENT INFECTIONS

Relatively few viruses cause persistent or latent infections.HBV,HCV, rabies virus, measles virus, HIV,HTLV,HPV, herpesviruses, and some poxviruses are notable exceptions. The mechanisms for persistent infection vary widely. In persistent HCV infection and to a lesser extent in HIV infection, the high mutation rates in viral genome

replication significantly facilitate persistent infection, continuously yielding mutant viruses that have lost antigenic determinants to which the host has developed effective immune responses. HIV is directly immunosuppressive, depleting CD4+ T lymphocytes and compromising CD8+ cytotoxic T cell immune responsiveness. Moreover, HIV encodes a Nef protein that downmodulates major histocompatibility complex (MHC) class I expression, rendering HIV-infected cells partially resistant to immune CD8+ cytolysis. The high mutation rate and the magnitude of virus load conspire to promote persistent infection with drug-resistant HIV mutants.

In contrast, herpesviruses and papovaviruses have much lower mutation rates. Their persistence is due to their ability to establish latent infection and to reactivate from latency. In this instance, *latency* is defined as a state of infection with a full viral genome replicated by cellular DNA polymerase in conjunction with the cell genome; there is no expression of viral genes associated with lytic infection and therefore no production of infectious virus. ForHPVs, latently infected basal epithelial cells replicate. Some of the progeny cells provide a stable supply of latently infected basal cells, while others go on to squamous differentiation and in the process become permissive for lytic virus infection. For herpesviruses, latent infection is established in nonreplicating neural cells (HSV andVZV) and in replicating cells of early hematopoietic lineages [EBV and probablyCMV,HHV-6, HHV-7, and Kaposi's sarcoma-associated herpesvirus (KSHV, also known as HHV-8)]. Reactivation from neural latency appears to be an intermittent process provoked by external stimuli, whereas reactivation from hematopoietic precursors appears to be a more continuous process. In their latent stage, HPV and herpesvirus genomes are hidden from the normal immune response. It is still not fully understood how latent and reactivated HPV and herpesvirus infections escape immediate and effective immune responses in highly immune hosts. HPV, HSV, and VZV may be somewhat protected because of their replication in middle and upper layers of the squamous epithelium. HSV and CMV are also known to encode proteins that downregulateMHCclass I expression and antigenic peptide presentation on infected cells, thereby enabling these cells to escape CD8+ T lymphocyte cytotoxicity. Latent infection and intermittent reactivation perpetuate HPV and herpesvirus infections in human populations by allowing the viruses to persist in immune hosts and to be transmitted to the next generation of naive hosts.

Like other poxviruses, molluscum contagiosum virus cannot establish latent infection but rather causes persistent infection in hypertrophic lesions that last for months or years. This virus encodes a chemokine homologue that probably blocks inflammatory responses and anMHCclass I analogue that may block cytotoxic T lymphocyte attack.

## PERSISTENT VIRAL INFECTIONS AND CANCER

Persistent viral infection is estimated to be the root cause of as many as 20% of human malignancies. For the most part, cancer is an accidental and highly unusual or long-term effect of infection with oncogenic human viruses. In these malignancies, viral infection is a critical and ultimately determinative early step, and an unusual virus-infected cell undergoes the subsequent genetic changes that permit the enhanced autonomous growth and survival characteristic of a malignant cell. Most hepatocellular carcinoma is now believed to be caused by chronic inflammatory, immune, and regenerative responses toHBV orHCVinfection. Epidemiologic data firmly link HBV and HCV infection

to hepatocellular carcinoma, and studies in murine experimental models indicate that chronic liver injury and repair induced by virus-encoded proteins can result in hepatocellular cancer. In rare instances, HBV DNA integrates into cellular DNA -- an event that probably contributes to the development of some tumors.

Almost all cervical carcinoma is caused by long-term persistent replication of "high-risk" genitalHPVstrains. An infrequent consequence of persistent HPV replication is the integration of a small fragment of the HPV genome encoding the HPV E6 and E7 proteins into chromosomal DNA. Overexpression of these proteins of HPV type 16 or 18 eliminates at least two major tumor-suppressive mechanisms in the infected cell and causes profound changes in cellular growth and survival. Nevertheless, subsequent chromosomal changes must occur over ensuing cycles of cell growth if a sufficiently malignant cell is to invade the surrounding tissues.

Similarly, long-termEBVinfection and expression of the EBV oncogene LMP1 in a clone of latently infected epithelial cells appears to be a critical early step in the evolution of anaplastic nasopharyngeal carcinoma, a common malignancy in Chinese and North African populations. High-level LMP1 expression is a hallmark of many cases of Hodgkin's disease. Among younger age groups, >50% of Hodgkin's disease tumors are clonally derived from an EBV-infected cell. TheHTLV-I Tax and Rex proteins appear to be critical to the initiation of cutaneous adult T cell lymphoma/leukemias that may occur long after primary HTLV-I infection.

A newEBV-related herpesvirus,KSHV, was identified in a search for the postulated sexually transmitted etiologic agent of Kaposi's sarcoma in HIV-infected individuals. Molecular data confirm the presence of KSHV DNA in all Kaposi's tumors, including those associated with HIV infection, transplantation, and familial transmission.

Evidence supporting a causal role of viral infection in these malignancies includes epidemiologic data, the presence of viral DNA in all tumor cells, the ability of the viruses to transform human cells in culture, the results of in vitro assays for transforming effects of specific viral genes on cell growth, and pathologic data indicating the expression of transforming viral genes in premalignant or malignant cells in vivo.

EBVis a unique example of a human virus that relies on the normal immune response to contain the potentially unrestrained growth of infected B lymphocytes. In the initial stages of normal primary EBV infection, EBV "latently" infects B lymphocytes and expresses at least eight viral proteins that cause continuous cell proliferation. The infected cells grow indefinitely in vitro or in T cell-deficient mice. Most of the viral proteins are highly antigenic, and these virus-infected cells, which can transiently constitute 10% of the circulating B lymphocyte population, are met with an overwhelming helper and cytotoxic T cell response during primary infection. The number of virus-infected cells then falls rapidly, and the one EBV-infected cell in a million that persists does not express most of the viral proteins that cause B cell proliferation. These persisting cells are the site of normal latent infection. Breakthrough growth of the EBV-infected B lymphocytes almost never occurs in immunocompetent hosts. However, in immunosuppressed AIDS patients or organ transplant recipients, EBV-infected B lymphocytes expressing the full set of growth-transforming genes may grow, uncontrolled by the immune system, and cause self-sustained and potentially fatal

lymphoproliferative disease. Clinical investigation has resulted in novel strategies for treating these virus-induced malignancies by increasing T cell responsiveness through ex vivo expansion and readministration of EBV-specific T cells and by attacking the proliferating B cells with antibody coupled to toxins.

## RESISTANCE TO VIRAL INFECTIONS

Resistance to viral infection is initially provided by factors that are not virus-specific. Physical protection is afforded by the cornified layers of the skin and by mucous secretions that continuously sweep over mucosal surfaces. Once the first cell is infected, viral infection inducesIFNs, which are important local resistance factors. Viral infection may also cause the release of other cytokines from infected cells. Viral protein epitopes expressed on the cell surface in the context ofMHCclass I and II HLA proteins attract T cells with appropriate receptors. Cytokines, inflammatory agents, and antigens released by virus-induced cell death attract inflammatory cells, dendritic cells, granulocytes, natural killer (NK) cells, and B lymphocytes to the sites of initial infection. IFNs and NK cells are particularly important in containing viral infection for the first several days. Granulocytes and macrophages are also important in the phagocytosis and degradation of viruses, especially after an initial antibody response.

Some 7 to 10 days after infection, virus-specific antibody responses, virus-specific HLA class II-restricted CD4+ helper T lymphocyte responses, and virus-specific HLA class I-restricted CD8+ cytotoxic T lymphocyte responses are detected. These responses, whose magnitude typically increases over the second and third weeks of infection, are important in rapid recovery. Between the second and third weeks of infection, the antibody type usually changes from IgM to IgG, and IgA antibody is detected at initially infected mucosal surfaces. Antibody may directly neutralize virus by binding to its surface and preventing its adsorption or penetration. Complement usually enhances virus neutralization. Antibody and complement can also lyse virus-infected cells that express viral proteins on their surface. A cell infected with an enveloped virus usually expresses viral envelope glycoprotein components on its surface and is thus rendered subject to destruction by antibodies and complement.

The antibody and CD4+/CD8+ T lymphocyte responses tend to persist for several months after primary infection. Antibody-producing lymphocytes persist in small numbers as memory cells and begin to proliferate rapidly in response to a second infection, providing an early barrier to reinfection with the same virus. Immunologic memory for T cell responses appears to be less long-lived, and redevelopment of T cell immunity may take longer than secondary antibody responses, particularly when many years have elapsed between primary infection and reexposure.

Some viruses have genes that alter innate and acquired host defenses. Adenoviruses encode small RNAs that inhibitIFNshutoff of infected-cell protein synthesis. Adenovirus E1A inhibits IFN-mediated changes in cell gene transcription. Adenovirus E3 proteins preventTNF-induced cytolysis and block HLA class I antigen synthesis by the infected cell.HSVICP47 andCMV US11 block class I antigen presentation.EBVencodes an interleukin (IL) 10 homologue that inhibitsNK and T cell responses. Vaccinia virus B15R is an IL-1 receptor decoy. Vaccinia virus B8R is a soluble TNF receptor that blocks the effects of TNF. Vaccinia virus CrmA inhibits the ability of CD8+ cytotoxic cells to kill

virus-infected cells. Some poxviruses and herpesviruses encode blockers of chemokines and thereby inhibit cellular inflammatory responses. The adoption of these strategies by viruses highlights the importance of these host resistance factors in containing viral infection as well as that of redundancy in host resistance. The ultimate success of a virus requires a live host to help it disseminate.

Much has been written about the role of specific aspects of the host immune response in containment of specific virus infections. Certainly, T lymphocyte disorders are associated with severe primary and reactivated herpesvirus infections, and antibody responses are important in resistance to many RNA virus infections. However, antibody responses are also important in resistance to herpesvirus infections, as is exemplified by the utility of immunoglobulin therapy in early amelioration of these infections. T lymphocyte responses play a significant role in resistance to RNA virus infections, as is illustrated by the presence of cytotoxic T cells specific for influenza virus nucleoprotein.

Host resistance does not come without a price. Clearly, aspects of the host response contribute to the pathophysiologic manifestations and symptoms of viral infection. Inflammation at sites of viral infection can increase rates of local cell death. Immune responses to viral infection can target related epitopes on normal cells. While such effects have been demonstrated in experimental models, their role in the autoimmune manifestations of primary or recurrent human viral infections is uncertain.

## INTERFERONS

All human cells can synthesizeIFN-aor -b in response to viral infection. The IFN response is usually induced by the presence of double-strand viral RNA, which can be made by both RNA and DNA viruses. IFN-g is not directly related to IFN-a or -b and is produced mainly byNK cells and by immune T lymphocytes responding toIL-12. IFN-a and -b bind to the IFN-a receptor, while IFN-gbinds to a different but related receptor. Both receptors signal through receptor-associated JAK kinases and other cytoplasmic proteins, including "STAT" proteins. These proteins are tyrosine phosphorylated by JAK kinases, translocate to the nucleus, and transactivate promoters for specific cell genes. Three types of antiviral effects are induced by IFN at the transcriptional level. The first effect is attributable to the induction of 2¢-5¢ oligo(A) synthetases, which require double-strand RNA for their activation. Activated synthetase polymerizes oligo(A) and thereby activates RNAse L, which in turn degrades single-strand RNA. The second effect takes place through the induction of PKR, a serine and threonine kinase that is also activated by double-strand RNA. PKR phosphorylates and negatively regulates the translational initiation factor eIF2-a, shutting down protein synthesis in the infected cell. A third effect is initiated through the induction of Mx proteins, a family of GTPases that is particularly important in inhibiting influenza virus and vesicular stomatitis virus replication. None of these IFN effects is directed specifically against the virus; infected-cell RNA and protein synthesis are globally inhibited. IFN probably contributes to the death of the infected cell.

## DIAGNOSTIC VIROLOGY

A wide variety of methods are now used to diagnose viral infection, but serology and viral isolation in tissue culture remain the backbone of diagnostic virology. Acute- and

convalescent-phase sera with rising antibody titers to virus-specific antigens and a shift from IgM to IgG antibodies are generally accepted as diagnostic of acute viral infection. Traditionally, virus-specific antibodies have been detected by hemadsorption, hemagglutination, or indirect immunofluorescence. Immunofluorescence assays use fixed virus-infected cells as a target for serum antibodies. Hemadsorption and hemagglutination assays measure the ability of serum antibodies to the hemagglutinin proteins of RNA viruses to inhibit virus-induced adsorption or agglutination. Serologic diagnosis is based on a greater-than-fourfold rise in IgG antibody concentration when acute- and convalescent-phase serum samples are analyzed at the same time. A simultaneous fall in IgM antibody confirms recent primary viral infection. Immunofluorescence, hemadsorption, and hemagglutination assays are labor-intensive and are being replaced by enzyme-linked immunosorbent assays (ELISAs). ELISAs generally use specific viral proteins purified from virus-infected cells or produced by recombinant DNA technology. These viral antigens are attached to a solid phase, where they can be incubated with serum, washed to eliminate nonspecific antibodies, and reacted with an enzyme-linked reagent to detect human IgG or IgM antibody specifically adhering to the viral antigen on the solid phase. The amount of antibody can then be quantitated by the intensity of a color reaction mediated by the linked enzyme. ELISAs can be automated and can have enhanced sensitivity. Western blots measure antibody to multiple viral proteins simultaneously. The proteins are separated by size and transferred to an inert membrane, where they are incubated with serum antibodies. Western blots have an internal specificity control, since the level of reactivity for viral proteins can be compared with that for cellular proteins in the same sample. Western blots are a useful confirmatory test but require individual evaluation and are inherently difficult to quantitate.

Viral isolation in tissue culture is dependent on the infection of susceptible cells and amplification through viral replication in infected cells. Virus growing in tissue culture cells can frequently be identified by its effect under light microscopy. For example,HSVproduces a typical cytopathic effect in rabbit kidney cells within 3 days. Other viral cytopathic effects may not be as diagnostically useful. Identification may require confirmation by staining with virus-specific monoclonal antibodies. Viruses growing in tissue culture can also be identified by hemadsorption, by interference (e.g., rubella virus-infected cells resist lysis by echovirus), or by electron microscopy (assuming that the specimen has altered cell morphology, as observed by ordinary light microscopy).

The efficiency and speed of virus identification can be enhanced by combining short-term culture with immune detection. In assays with "shell vials" of tissue culture cells growing on a coverslip, viral infection can be detected by staining of the culture with a monoclonal antibody to a specific viral protein expressed early in viral replication. Thus, virus-infected cells can be detected within hours or days of inoculation -- before the several rounds of infection that would be required to produce a visible cytopathic effect.

The sensitivity of virus isolation depends on the collection of specimens from the appropriate site and the rapid transport of these specimens in the appropriate medium to the virology laboratory. Rapid transport maintains viral viability and limits bacterial and fungal overgrowth. Lipid-enveloped viruses are generally much more sensitive to

freezing and thawing than nonenveloped viruses. The most appropriate site for culture depends on the pathogenesis of the virus in question. Nasopharyngeal, tracheal, or endobronchial aspirates are most appropriate for the identification of respiratory viruses. Sputum cultures generally are not appropriate because bacterial contamination and viscosity threaten tissue-culture cell viability. Aspirates of vesicular fluid are useful for isolation ofHSV andVZV. Nasopharyngeal aspirates and stool specimens may be useful when the patient has fever and a rash and an enteroviral infection is suspected. Adenoviruses can be cultured from the urine of patients with hemorrhagic cystitis.CMV can frequently be isolated from cultures of urine or buffy coat. Biopsy material can be effectively cultured when viruses infect major organs, as in HSV encephalitis or adenovirus pneumonia. Unlike serology, the isolation of a virus does not establish the time of primary infection. Many viruses persistently or intermittently colonize normal human mucosal surfaces. Saliva is not infrequently positive for herpesviruses, and 1% of normal urine samples are positive for CMV. Isolations from blood, cerebrospinal fluid (CSF), or biopsy specimens are more often diagnostic of significant virus infection.

Another method aimed at increasing the speed of viral diagnosis is direct antigen testing. Virus-infected cells obtained directly from the patient are detected by staining with virus-specific monoclonal antibodies; for example, epithelial cells obtained by nasopharyngeal aspiration can be stained with a variety of monoclonal antibodies to respiratory viruses. The Tzanck preparation used to detect multinucleated giant cells inHSV- orVSV-induced lesions was the predecessor of these direct antigen tests and can be enhanced by the use of HSV- or VZV-specific monoclonal antibodies. Similarly, monoclonal antibodies can be applied to histopathology specimens to identify virus-infected cells.

Advances in nucleic acid technology are revolutionizing diagnostic virology. The speed and sensitivity of tests that directly amplify minute amounts of viral nucleic acids present in specimens mean that detection no longer depends on viable virus and its replication. For example, amplification and detection ofHSVnucleic acids leaking into theCSF of patients with HSV encephalitis can be more sensitive than culture of virus from CSF. The extreme sensitivity of these tests can be a problem, since trivial amounts of contamination can lead to false-positive results. In addition, detection of viral nucleic acids does not necessarily indicate virus-induced disease, especially in cases where viruses (e.g., herpesviruses) can cause persistent asymptomatic infection.

Measurement of the amount of viral RNA or DNA in peripheral blood is becoming an important means for determining which patients are at increased risk for virus-induced disease and for evaluating clinical responses to antiviral chemotherapy. Direct staining withCMV-specific monoclonal antibodies to quantitate virus-infected cells in the peripheral blood or CMV antigenemia can be useful in identifying which immunosuppressed patients may be at risk for CMV-induced disease. New CMV assays using nucleic acid technologies for the same purpose have been approved for clinical use. RNA viral-load measurements by nucleic acid technologies are now routinely used in AIDS patients to evaluate responses to an increasing number of antiviral agents. Viral-load measurements may also be useful for evaluating the treatment of patients withHBV andHCVinfections.

The use of antiviral agents for the treatment of herpesvirus and HIV infections has been

highly effective. However, the emergence of drug-resistant HIV strains in treated patients can limit efficacy in some cases. The increased number of antiviral agents and drug classes with different viral targets has made the identification of drug-resistant viruses clinically relevant, especially for HIV infection. Drug resistance in herpesviruses is a more unusual problem.

Viral genotyping is a new and faster method for the identification of drug-resistant viruses. Rising viral loads despite antiviral chemotherapy may indicate emergence of resistant HIV strains. Resistance to reverse transcriptase or protease inhibitors has been associated with specific mutations in the reverse transcriptase or protease genes. Identification of these mutations by polymerase chain reaction amplification and nucleic acid sequencing can be clinically useful for determining which antiviral agents may still be effective. Genotyping ofHCV may also help identify patients who can benefit from combination chemotherapy.

Viral phenotyping may also be useful for identifying resistant viruses associated with new or unrecognized genetic mutations. These labor-intensive assays are not routinely available, but technical advances and continued evolution of drug-resistant viruses may make these tests more clinically relevant in the near future.

**IMMUNIZATION FOR THE PREVENTION OF VIRAL INFECTIONS**

Viral vaccines were among the outstanding accomplishments of twentieth-century science. The scourge of smallpox has been eradicated. Poliovirus eradication may soon follow. Rabies and measles can be contained or eliminated. Excess mortality due to influenza virus epidemics can be contained, and the threat of influenza pandemics has decreased. WidespreadHBVvaccination has dramatically lessened the frequency of acute and chronic hepatitis and is expected to lead to a dramatic decrease in the incidence of hepatocellular carcinoma. The ease with which some viruses are attenuated in tissue culture has led to widespread immunization against rubella, measles, mumps, and chickenpox. Recombinant DNA-based strategies will make it possible to prevent severe infections with many other viruses by using purified proteins or genetically engineered live virus vaccines. Unfortunately, there are limits to these prospects. The evolutionary divergence of HIV andHCV, for example, complicates the development of highly effective immunogens for the prevention of infection with these agents. Modestly effective immunogens that incorporate multiple B and T cell epitopes may prove useful for low-level exposures.

(Bibliography omitted in Palm version)

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Back to Table of Contents

## 181. ANTIVIRAL CHEMOTHERAPY, EXCLUDING ANTIRETROVIRAL DRUGS - *Raphael Dolin*

The development of drugs for antiviral chemotherapy and chemoprophylaxis is a relatively recent but now very active area of biomedical research. Significant progress has been made in recent years on new drugs for several viral infections. Despite these advances, the field of antiviral therapy -- both the number of antiviral drugs and our understanding of their optimal use -- continues to lag behind the field of antibacterial drug treatment, in which more than 60 years of experience have now been accumulated.

The development of antiviral drugs poses several challenges. Viruses replicate intracellularly and often employ host cell enzymes, macromolecules, and organelles for synthesis of viral particles. Therefore, useful antiviral compounds must discriminate between host and viral functions with a high degree of specificity; agents without such selectivity are likely to be too toxic for clinical use.

The development of laboratory assays to assist clinicians in the appropriate use of antiviral drugs is also in its infancy. Phenotypic and genotypic assays for resistance to antiviral drugs are becoming more widely available, and correlations of laboratory results with clinical outcomes in various settings are beginning to be defined. Of particular note has been the development of highly sensitive and specific methods to measure the concentration of virus in blood (*virus load*), which permit direct assessment of the antiviral effect of a given drug regimen in the host. Virus load measurements have been useful in recognizing the risk of disease progression in patients with certain viral infections and in identifying patients in whom antiviral chemotherapy might be of greatest benefit. Like any in vitro laboratory test, these tests yield results that are highly dependent on (and likely to vary with) the laboratory techniques employed.

Information regarding the pharmacokinetics of some antiviral drugs, particularly in diverse clinical settings, is limited. Assays to measure the concentrations of these drugs, especially of their active moieties within cells, are not widely available. Thus, there are relatively few guidelines for adjusting dosages of antiviral agents to maximize antiviral activity and minimize toxicity. Clinical use of antiviral drugs must therefore be accompanied by particular vigilance with regard to unanticipated adverse effects.

Like that of other infections, the course of viral infections is profoundly affected by an interplay of the pathogen with a complex set of host defenses. The presence or absence of preexisting immunity and the ability to mount humoral and/or cell-mediated immune responses are important determinants of the outcome of viral infections. The state of the host's defenses needs to be considered when antiviral agents are utilized or evaluated.

As with any therapy, the optimal use of antiviral compounds requires a specific and timely diagnosis. For some viral infections, such as herpes zoster, the clinical manifestations are so characteristic that a diagnosis can be made on clinical grounds alone. For other viral infections, such as influenza A, epidemiologic information (e.g., the documentation of a community-wide outbreak) can be used to make a presumptive diagnosis with a high degree of accuracy. However, for most other viral infections, including herpes simplex encephalitis, cytomegaloviral infections other than retinitis, and

enteroviral infections, diagnosis on clinical grounds alone cannot be accomplished with certainty. For such infections, rapid viral diagnostic techniques are of great importance. Considerable progress has been made in recent years in the development of such tests, which are now widely available for a number of viral infections.

Despite these complexities, the efficacy of a number of antiviral compounds has been clearly established in rigorously conducted and controlled studies. As summarized inTable 181-1, this chapter reviews the antiviral drugs that are currently approved or are likely to be considered for approval in the near future for use against viral infections other than those caused by HIV. Antiretroviral drugs are reviewed inChap. 309.

## ANTIVIRAL DRUGS ACTIVE AGAINST RESPIRATORY INFECTIONS

### AMANTADINE AND RIMANTADINE

Amantadine and the closely related compound rimantadine are primary symmetric amines. Their antiviral activity is limited to influenza A viruses, whose replication they inhibit by interfering with the uncoating of virus after infection of the cell. This interference is attributable to the agents' interaction with the influenza A M2 matrix protein, during which the ion channel function of M2 is inhibited. A substitution of a single amino acid in the M2 protein can result in a virus that is resistant to amantadine and rimantadine.

Amantadine and rimantadine have been demonstrated to be effective in the prophylaxis of influenza A in large-scale studies of young adults and in less extensive studies of children and elderly subjects. In such studies, efficacy rates of 55 to 80% in the prevention of influenza-like illness were noted, and even higher rates were reported when virus-specific attack rates were calculated. Amantadine and rimantadine have also been demonstrated to be effective in the treatment of influenza A infection in studies involving predominantly young adults and, to a lesser extent, children. Administration of these compounds within 24 to 72 h after the onset of illness has resulted in a reduction of the duration of signs and symptoms by ~50% from that in a placebo-treated group. The effect on signs and symptoms of illness is superior to that of commonly used antipyretic-analgesics. Only anecdotal reports are available concerning the efficacy of amantadine or rimantadine in the prevention or treatment of complications of influenza (e.g., pneumonia).

Amantadine and rimantadine are available only in oral formulations and are ordinarily administered to adults once or twice daily in a dose of 100 to 200 mg/d. Despite their structural similarities, the pharmacokinetics of the two compounds are different. Amantadine is not metabolized and is excreted almost entirely by the kidney, with a half-life of 12 to 17 h and peak plasma concentrations of 0.4 ug/mL. Rimantadine is extensively metabolized to hydroxylated derivatives and has a half-life of 30 h. Only 30 to 40% of an orally administered dose is recovered in the urine. The peak plasma levels of rimantadine are approximately half those of amantadine, but rimantadine is concentrated in respiratory secretions to a greater extent than amantadine. For prophylaxis, the compounds must be administered daily for the period at risk (i.e., the peak duration of the outbreak). For therapy, amantadine or rimantadine is generally administered for 5 to 7 days.

Although these compounds are generally well tolerated, 5 to 10% of amantadine recipients experience mild central nervous system side effects consisting primarily of dizziness, anxiety, insomnia, and difficulty in concentrating. These effects are rapidly reversible upon cessation of the drug's administration. At a dose of 200 mg/d, rimantadine is better tolerated than amantadine; in a large-scale study of young adults, adverse effects were no more frequent among rimantadine recipients than among placebo recipients. Seizures and worsening of congestive heart failure have also been reported in patients treated with amantadine, although a causal relationship has not been established. The dosage of amantadine should be reduced to £100 mg/d in patients with renal insufficiency [i.e., a creatinine clearance ($Cr_{Cl}$) rate of <50 mL/min] and in the elderly. A rimantadine dose of 100 mg/d should be used for patients with a $Cr_{Cl}$ of<10 mL/min and in the elderly. Resistance to amantadine and rimantadine can be induced readily in vitro. The emergence and probable transmission of virus resistant to these drugs have also been noted in vivo after their use for the treatment of children or adults. In the United States, both amantadine and rimantadine are approved for the prophylaxis and treatment of influenza A in adults and for prophylaxis in children. Amantadine is also approved for the treatment of influenza A in children.

**RIBAVIRIN**

Ribavirin is a synthetic nucleoside analogue that inhibits a wide range of RNA and DNA viruses. The mechanism of action of ribavirin is not completely defined and may be different for different groups of viruses. Ribavirin-5¢-monophosphate blocks the conversion of inosine-5¢-monophosphate to xanthosine-5¢-monophosphate and interferes with the synthesis of guanine nucleotides as well as that of both RNA and DNA. Ribavirin-5¢-monophosphate also inhibits capping of virus-specific messenger RNA in certain viral systems. In studies demonstrating the effectiveness of ribavirin, the compound has been administered as a small-particle aerosol. It has been used to treat respiratory syncytial virus (RSV) infections in infants and -- less extensively -- to treat parainfluenza virus infections in children and influenza A and B virus infections in young adults. In infants with RSV infection who were given ribavirin by continuous aerosol for 3 to 6 days, illness and lower respiratory tract signs resolved more rapidly and arterial oxygen desaturation was less pronounced than in placebo-treated groups. Ribavirin has also had a beneficial clinical effect in infants with RSV infection who require mechanical ventilation. Aerosolized ribavirin has been administered to older children and adults with severe RSV and parainfluenza virus infections (including immunosuppressed patients), but the benefit of this treatment, if any, is unclear. In RSV infections, ribavirin is often given in combination with immunoglobulins.

Orally administered ribavirin has not been effective in the treatment of influenza A virus infections. Intravenous or oral ribavirin has reduced mortality among patients with Lassa fever; it has been particularly effective in this regard when given within the first 6 days of illness. Intravenous ribavirin has been reported to be of clinical benefit in the treatment of hemorrhagic fever with renal syndrome caused by Hantaan virus and as therapy for Argentinian hemorrhagic fever. Moreover, oral ribavirin has been recommended for the treatment and prophylaxis of Congo-Crimean hemorrhagic fever. Intravenous ribavirin is being evaluated as therapy for the hemorrhagic fever with pulmonary syndrome caused by newly described hantaviruses in the United States. Oral administration of ribavirin

reduces serum aminotransferase levels in patients with chronic hepatitis C virus (HCV) infection; since it appears not to reduce serum HCV RNA levels, the mechanism of this effect is unclear. Given in doses of 1000 to 1200 mg/d in combination with interferon (IFN)a (see below), ribavirin has been approved for the treatment of patients with chronic HCV infection.

Large doses of ribavirin administered orally (800 to 1000 mg/d) have been associated with reversible hematopoietic toxicity. This effect has not been observed with aerosolized ribavirin, apparently because little drug is absorbed systemically. Aerosolized administration of ribavirin is generally well tolerated but occasionally is associated with bronchospasm, rash, or conjunctival irritation. Aerosolized ribavirin has been licensed for treatment ofRSVinfection in infants and should be administered under close supervision -- particularly in the setting of mechanical ventilation, where precipitation of the drug is possible. Health care workers exposed to the drug have experienced minor toxicity, including eye and respiratory tract irritation. Because ribavirin is mutagenic, teratogenic, and embryotoxic, its use is generally contraindicated in pregnancy. Its administration as an aerosol poses a risk to pregnant health care workers.

**ZANAMIVIR AND OSELTAMIVIR**

Influenza viral neuraminidase is essential for release of the virus from infected cells and for its subsequent spread throughout the respiratory tract of the infected host. The enzyme cleaves terminal sialic acid residues, thus destroying the cellular receptors recognized by the viral hemagglutinin. Zanamivir, a sialic acid analogue, is a highly active and specific inhibitor of the neuraminidases of influenza A and B viruses. Oseltamivir is another neuraminidase inhibitor that is a transition-state analogue of sialic acid cleavage. Its antineuraminidase activity is similar to that of zanamivir. Oseltamivir phosphate is an ethyl ester prodrug that is converted to oseltamivir carboxylate by esterases in the liver. Both zanamivir and oseltamivir act through competitive and reversible inhibition of the active site of influenza A and B viral neuraminidases and have relatively little effect on mammalian cell enzymes. As would be expected from their different mechanisms of action, zanamivir and oseltamivir are active against strains of influenza A virus that are resistant to amantadine and rimantadine.

Zanamivir has low oral bioavailability. It is inhaled orally via a hand-held inhaler. By this route, ~15% of the dose is deposited in the lower respiratory tract, and low plasma levels of the drug are detected. Orally administered oseltamivir has an oral bioavailability of >60% and a plasma half-life of 7 to 9 h. The drug is excreted unmetabolized, primarily by the kidney.

Intranasal inhaled zanamivir is generally well tolerated. The most frequent toxicities encountered with orally administered oseltamivir are nausea, gastrointestinal discomfort, and (less commonly) vomiting. Gastrointestinal discomfort is usually transient and is less likely if the drug is administered with food. No serious clinical or laboratory toxicities have yet been reported with zanamivir or oseltamivir in clinical trials.

Inhaled zanamivir and orally administered oseltamivir have been effective in the treatment of naturally occurring influenza A or B in otherwise healthy adults. In

placebo-controlled studies, illness has been shortened by 1 to 1.5 days of therapy with either of these drugs. Once-daily inhaled zanamivir or orally administered oseltamivir provides effective prophylaxis against laboratory-documented influenza A-associated illness. The emergence of viruses resistant to zanamivir or oseltamivir appears to be infrequent in clinical studies carried out thus far.

As of this writing, zanamivir and oseltamivir have been approved by the U.S. Food and Drug Administration (FDA) for treatment of influenza in adults (and -- in the case of zanamivir -- in children³7 years of age) who have been symptomatic for£2 days. Indications for prophylactic use are under review.

## ANTIVIRAL DRUGS ACTIVE AGAINST HERPESVIRUS INFECTIONS

### ACYCLOVIR AND VALACYCLOVIR

Acyclovir is a highly potent and selective inhibitor of the replication of certain herpesviruses, including herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV). It is relatively ineffective in the treatment of human cytomegalovirus (CMV) infections; however, some studies have indicated its effectiveness in the prevention of CMV-associated disease in immunosuppressed patients. Valacyclovir, the L-valyl ester of acyclovir, is converted almost entirely to acyclovir after oral administration. Valacyclovir has pharmacokinetic advantages over orally administered acyclovir: it exhibits significantly greater oral bioavailability, results in higher blood levels, and can be given less frequently than acyclovir.

The high degree of selectivity of acyclovir is related to its mechanism of action, which requires that the compound first be phosphorylated to acyclovir monophosphate. This phosphorylation occurs efficiently in herpesvirus-infected cells by means of a virus-coded thymidine kinase. In uninfected mammalian cells, little phosphorylation of acyclovir occurs, and the drug is therefore concentrated in herpesvirus-infected cells. Acyclovir monophosphate is subsequently converted by host cell kinases to a triphosphate that is a potent inhibitor of virus-induced DNA polymerase but has relatively little effect on host cell DNA polymerase. Acyclovir triphosphate can also be incorporated into viral DNA, with early chain termination.

Acyclovir is available in intravenous, oral, and topical forms, while valacyclovir is available in an oral formulation. Intravenous acyclovir is markedly effective in the treatment of mucocutaneousHSVinfections in immunocompromised hosts, reducing time to healing, duration of pain, and virus shedding. When administered prophylactically during periods of intense immunosuppression (e.g., related to chemotherapy for leukemia or transplantation) and before the development of lesions, intravenous acyclovir reduces the frequency of HSV-associated disease. After prophylaxis is discontinued, HSV lesions recur. Intravenous acyclovir is also effective in the treatment of HSV encephalitis; two comparative trials have indicated that acyclovir is more effective than vidarabine for this indication (see below). BecauseVZV is generally less sensitive to acyclovir than is HSV, higher doses of acyclovir must be used to treat VZV infections. In immunocompromised patients with herpes zoster, intravenous acyclovir reduces the frequency of cutaneous dissemination and visceral complications and -- in one comparative trial -- was more effective than vidarabine. Acyclovir,

administered orally at doses of 800 mg five times a day, had a modest beneficial effect on localized herpes zoster lesions in both immunocompromised and immunocompetent patients. Combination of acyclovir with a tapering regimen of prednisone appeared to be more effective than acyclovir alone in terms of quality-of-life outcomes in immunocompetent herpes zoster patients over age 50. A comparative study of acyclovir (800 mg orally five times daily) and valacyclovir (1 g orally tid) in immunocompetent patients with herpes zoster indicated that the latter drug may be more effective in eliciting the resolution of zoster-associated pain. Orally administered acyclovir (600 mg five times a day) reduced complications of herpes zoster ophthalmicus in a placebo-controlled trial.

In normal children with chickenpox, acyclovir -- administered at 20 mg/kg qid, up to a maximum of 800 mg qid, within 24 h of the onset of rash -- resulted in a modest overall clinical benefit. Intravenous acyclovir has also been reported to be effective in the treatment of immunocompromised children with chickenpox.

The most widespread use of acyclovir is in the treatment of genitalHSVinfections. Intravenous or oral acyclovir or oral valacyclovir has shortened the duration of symptoms, reduced virus shedding, and accelerated healing when employed for the treatment of primary genital HSV infections. Oral acyclovir and valacyclovir have also had a modest effect in treatment of recurrent genital HSV infections. However, the failure of treatment of either primary or recurrent disease to reduce the frequency of subsequent recurrences has indicated that acyclovir is ineffective in eliminating latent infection. Chronic oral administration of acyclovir for periods of 1 to 6 years or longer or of valacyclovir for up to 1 year has reduced the frequency of recurrences markedly during therapy; once the drug is discontinued, lesions recur. In AIDS patients, chronic or intermittent administration of acyclovir has been associated with the development of HSV andVZVstrains resistant to the action of the drug and with clinical failures. The most common mechanism of resistance is a deficiency of the virus-induced thymidine kinase. Patients with HSV or VZV infections resistant to acyclovir have frequently responded to foscarnet.

With the availability of the oral and intravenous forms, there are few indications for topical acyclovir, although treatment with this formulation has been modestly beneficial in primary genitalHSVinfections and in mucocutaneous HSV infections in immunocompromised hosts.

Overall, acyclovir is remarkably well tolerated and is generally free of toxicity. The most frequently encountered form of toxicity is renal dysfunction, particularly after rapid intravenous administration or with inadequate hydration. Central nervous system changes, including lethargy and tremors, are occasionally reported, primarily in immunosuppressed patients. However, whether these changes are related to acyclovir, to concurrent administration of other therapy, or to underlying infection remains unclear. Acyclovir is excreted primarily unmetabolized by the kidney, via both glomerular filtration and tubular secretion. Approximately 15% of a dose of acyclovir is metabolized to 9-[(carboxymethoxy)methyl]guanine or other minor metabolites. Reduction in dosage is indicated in patients with a $Cr_{Cl}$ of<50 mL/min per 1.73 $m_2$. The half-life of acyclovir is ~3 h in normal adults, and the peak plasma concentration after a 1-h infusion of a dose of 5 mg/kg is 9.8 ug/mL. Approximately 22% of an orally administered acyclovir dose is

absorbed, and peak plasma concentrations of 0.3 to 0.9 ug/mL are attained after administration of a 200-mg dose. Acyclovir penetrates relatively well into the cerebrospinal fluid (CSF), with concentrations approaching half of those found in plasma.

Acyclovir causes chromosomal breakage at high doses, but its administration to pregnant women has not been associated with fetal abnormalities. Nonetheless, the potential risks and benefits of acyclovir should be carefully assessed before the drug is used in pregnancy.

Valacyclovir exhibits three to five times greater bioavailability than acyclovir. The concentration-time curve for valacyclovir, given as 1 g orally tid, is similar to that for acyclovir, given as 5 mg/kg intravenously every 8 h. The safety profiles of valacyclovir and acyclovir are similar, although thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome has been reported in immunocompromised patients who have received high doses of valacyclovir. Valacyclovir is approved for the treatment of herpes zoster and for initial and recurrent episodes of genitalHSVinfections in immunocompetent adults as well as for suppressive treatment of genital herpes. It is being studied for use against other herpesvirus infections in various clinical settings.

**CIDOFOVIR**

Cidofovir is a phosphonate nucleotide analogue of cytosine. Its major use is inCMVinfections, particularly retinitis, but it is active against a broad range of herpesviruses, includingHSV, human herpesvirus (HHV) type 6, HHV-8, and certain other DNA viruses such as polyomaviruses, papillomaviruses, and adenoviruses. Cidofovir does not require initial phosphorylation by virus-induced kinases; the drug is phosphorylated by host cell enzymes to cidofovir diphosphate, which is a competitive inhibitor of viral DNA polymerases and, to a lesser extent, of host cell DNA polymerases. Incorporation of cidofovir diphosphate slows or terminates nascent DNA chain elongation. Cidofovir is active against HSV isolates that are resistant to acyclovir because of absent or altered thymidine kinase and against CMV isolates that are resistant to ganciclovir because of UL97 mutations. Cidofovir is usually active against foscarnet-resistant CMV, although cross-resistance to foscarnet as well as to ganciclovir has been described.

Cidofovir has poor oral availability and is administered intravenously. It is excreted primarily by the kidney and has a plasma half-life of 2.6 h. Cidofovir diphosphate's intracellular half-life of >48 h is the basis for the recommended dosing regimen of 5 mg/kg twice a week for the initial 2 weeks and then 5 mg/kg once a week. The major toxic effect of cidofovir is proximal renal tubular injury, as manifested by elevated serum creatinine levels and proteinuria. The risk of nephrotoxicity can be reduced by vigorous saline hydration and by concomitant oral administration of probenecid. Neutropenia, rashes, and gastrointestinal tolerance may also occur.

Intravenous cidofovir has been approved for the treatment ofCMVretinitis in AIDS patients who are intolerant of ganciclovir or foscarnet or in whom those drugs have failed. In a controlled study, a maintenance dosage of 5 mg/kg a week administered to AIDS patients reduced the progression of CMV retinitis from that seen at 3 mg/kg.

Intravenous cidofovir has been reported anecdotally to be effective therapy for acyclovir-resistant mucocutaneousHSVinfections. Likewise, topically administered cidofovir is reportedly beneficial against these infections in HIV patients; it is also being studied for the treatment of anogenital warts. Intravenous cidofovir is being evaluated as therapy for progressive multifocal leukoencephalopathy and for Kaposi's sarcoma. An ophthalmic formulation is being studied as treatment for adenoviral keratoconjunctivitis. Intravitreal cidofovir has been used to treat CMV retinitis but has been associated with significant toxicity.

**FOMIVIRSEN**

Fomivirsen is the first antisense oligonucleotide approved by the U.S. Food and Drug Administration (FDA) for therapy in humans. This phosphorothioate oligonucleotide, 21 nucleotides in length, inhibitsCMVreplication through interaction with CMV messenger RNA. Fomivirsen is complementary to messenger transcripts of the major immediate early region 2 (IE2) of CMV, which codes for proteins regulating viral gene expression. In addition to its antisense mechanism of action, fomivirsen may exert activity against CMV through inhibition of viral adsorption to cells as well as direct inhibition of viral replication. Because of its different mechanism of action, fomivirsen is active against CMV isolates that are resistant to nucleoside or nucleotide analogues, such as ganciclovir, foscarnet, or cidofovir.

Fomivirsen has been approved for intravitreal administration in the treatment ofCMVretinitis in AIDS patients who have failed to respond to other treatments or cannot tolerate them. Injections of 330 mg every 2 weeks have resulted in significant reductions in the rate of progression of CMV retinitis. The major toxicity is ocular inflammation, including vitritis and iritis, which usually responds to topically administered glucocorticoids.

**GANCICLOVIR**

An analogue of acyclovir, ganciclovir is active againstHSV andVZV and is markedly more active than acyclovir againstCMV. Ganciclovir triphosphate inhibits CMV DNA polymerase and can be incorporated into CMV DNA, whose elongation it eventually terminates. In HSV- and VZV-infected cells, ganciclovir is phosphorylated by virus-encoded thymidine kinases; in CMV-infected cells, it is phosphorylated by a viral kinase encoded by the UL97 gene. Ganciclovir triphosphate is present in tenfold higher concentrations in CMV-infected cells than in uninfected cells. Ganciclovir is approved for the treatment of CMV retinitis in immunosuppressed patients and for the prevention of CMV disease in transplant recipients. It is widely used for the treatment of other CMV-associated syndromes, including pneumonia, esophagogastrointestinal infections, hepatitis, and "wasting" illness.

Ganciclovir is available for intravenous or oral administration. Because its oral bioavailability is low (5 to 9%), relatively large doses (1 g tid) must be administered by this route. Oral bioavailability is enhanced if the drug is administered with food, as recommended. The serum half-life of ganciclovir is 3.5 h after intravenous administration and 4.5 h after oral administration. The drug is excreted primarily by the kidney in unmetabolized form, and its dosage should be reduced in cases of renal

failure. The most commonly employed dosage for initial therapy -- 5 mg/kg intravenously every 12 h for 14 to 21 days -- is followed by a maintenance dose of 5 mg/kg intravenously per day or 5 times per week, possibly for as long as immunosuppression persists. Oral ganciclovir is approved as an alternative to the intravenous preparation in maintenance therapy forCMVretinitis, where it appears to be somewhat less effective although more convenient than intravenous therapy. Intraocular ganciclovir, given by either intravitreal injection or intraocular implantation, has also been used to treat CMV retinitis.

Ganciclovir is effective as prophylaxis againstCMV-associated disease in organ and bone marrow transplant recipients. Oral ganciclovir administered prophylactically to AIDS patients with CD4+ counts of<100/uL provided protection against the development of CMV retinitis in one large-scale study and was subsequently approved for that indication. However, the long-term benefits of this approach to prophylaxis are unestablished, and most experts do not recommend the use of oral ganciclovir for that purpose.

The administration of ganciclovir has been associated with profound bone marrow suppression, particularly neutropenia, which significantly limits the drug's use in many patients. Bone marrow toxicity is potentiated when other bone marrow suppressants, such as zidovudine, are used concomitantly.

Resistance has been noted inCMVisolates obtained after therapy with ganciclovir, especially in patients with AIDS. Such resistance may develop through a mutation in either the viral UL97 gene or the viral DNA polymerase. Ganciclovir-resistant isolates are usually sensitive to foscarnet (see below).

**FAMCICLOVIR AND PENCICLOVIR**

Famciclovir is the diacetyl 6-deoxyester of the guanosine analogue penciclovir. Famciclovir is well absorbed orally, with a bioavailability of 77%, and is rapidly converted by deacetylation and oxidation to penciclovir. Penciclovir's spectrum of activity and mechanism of action are similar to those of acyclovir; thus penciclovir is not active against acyclovir-resistant viruses. Penciclovir is phosphorylated initially by a virus-encoded thymidine kinase and subsequently by cellular kinases to penciclovir triphosphate, which inhibitsHSV-1, HSV-2, andVZV DNA polymerases as well as hepatitis B virus (HBV). The serum half-life of penciclovir is 2 h, but the intracellular half-life of penciclovir triphosphate is 7 to 20 h -- markedly longer than that of acyclovir triphosphate. Penciclovir is eliminated primarily in the urine by both glomerular filtration and tubular secretion. The usually recommended dosage interval should be adjusted for renal insufficiency.

Clinical trials involving immunocompetent adults with herpes zoster showed that famciclovir was superior to placebo in eliciting the resolution of skin lesions and virus shedding and in shortening the duration of postherpetic neuralgia; moreover, it was at least as effective as acyclovir administered orally at a dose of 800 mg five times daily. Famciclovir was also effective in the treatment of herpes zoster in immunosuppressed patients. Clinical trials have demonstrated its effectiveness in suppression of genitalHSVinfections for up to 1 year and in the treatment of initial and recurrent

episodes of genital herpes. Famciclovir is effective as therapy for mucocutaneous HSV infections in HIV-infected patients. Application of a 1% penciclovir cream reduces the duration of signs and symptoms of herpes labialis in immunocompetent patients (by 0.5 to 1.0 day) and has been approved for that purpose by theFDA. Famciclovir is generally well tolerated, with occasional headache, nausea, and diarrhea reported in frequencies similar to those among placebo recipients. The administration of high doses of famciclovir for 2 years was associated with an increased incidence of mammary adenocarcinomas in female rats, but the clinical significance of this effect is unknown. Intravenous penciclovir is being investigated for the treatment of mucocutaneous HSV infections in immunosuppressed patients.

**FOSCARNET**

Foscarnet (phosphonoformic acid) is a pyrophosphate-containing compound that potently inhibits herpesviruses, includingCMV. This drug inhibits DNA polymerases at the pyrophosphate binding site at concentrations that have relatively little effect on cellular polymerases. Foscarnet does not require phosphorylation to exert its antiviral activity and is therefore active againstHSV andVZVisolates that are resistant to acyclovir because of deficiencies in thymidine kinase as well as against most ganciclovir-resistant strains of CMV. Foscarnet also inhibits the reverse transcriptase of HIV and is active against HIV in vivo.

Foscarnet is poorly soluble and must be administered intravenously via an infusion pump in a dilute solution over 1 to 2 h. The plasma half-life of foscarnet is 3 to 5 h and increases with decreasing renal function, since the drug is eliminated primarily by the kidneys. It has been estimated that 10 to 28% of a dose may be deposited in bone, where it can persist for months. The most common initial dosage of foscarnet -- 60 mg/kg every 8 h for 14 to 21 days -- is followed by a maintenance dose of 90 to 120 mg/kg once a day.

Foscarnet is approved for the treatment ofCMVretinitis in patients with AIDS and of acyclovir-resistant mucocutaneousHSVinfections. In a comparative clinical trial, the drug appeared to be about as efficacious as ganciclovir against CMV retinitis but was associated with a longer survival period, possibly because of its anti-HIV activity. Intraocular foscarnet has been used to treat CMV retinitis. Foscarnet has also been employed to treat acyclovir-resistant HSV andVZVinfections as well as ganciclovir-resistant CMV infections, although resistance to foscarnet has been reported in CMV isolates obtained during therapy.

The major form of toxicity associated with foscarnet is renal impairment. Thus renal function should be monitored closely, particularly during the initial phase of therapy. Since foscarnet binds divalent metal ions, hypocalcemia, hypomagnesemia, hypokalemia, and hypo- or hyperphosphatemia can develop. Saline hydration and slow infusion appear to protect the patient against nephrotoxicity and electrolyte disturbances. Although hematologic abnormalities have been documented (most commonly anemia), foscarnet is not generally myelosuppressive and may be administered concomitantly with myelosuppressive medications such as zidovudine.

**IDOXURIDINE**

Idoxuridine inhibits the replication of herpesviruses and poxviruses. It was formerly used systemically to treat herpesvirus infections, but, because of associated toxicity and lack of proven efficacy, its systemic use has largely been abandoned. Topical idoxuridine is effective in the treatment ofHSVkeratitis, particularly in superficial infections, but has been supplanted by topically applied trifluridine and vidarabine (see below).

## TRIFLURIDINE

Trifluridine is a pyrimidine nucleoside active againstHSV-1, HSV-2, andCMV. Trifluridine monophosphate irreversibly inhibits thymidylate synthetase, and trifluridine triphosphate inhibits viral and, to a lesser extent, cellular DNA polymerases. Because of systemic toxicity, its use is limited to topical therapy. Trifluridine is approved for treatment of HSV keratitis, for which trials have shown that it is more effective than topical idoxuridine but similarly effective to topical vidarabine. The drug has benefited some patients with HSV keratitis who have failed to respond to idoxuridine or vidarabine. Topical application of trifluridine to sites of acyclovir-resistant HSV mucocutaneous infections has also been beneficial in some cases.

## VIDARABINE

Vidarabine is a purine nucleoside analogue with activity againstHSV-1, HSV-2,VZV, andEBV. Vidarabine inhibits viral DNA synthesis through its 5¢-triphosphorylated metabolite, although its precise molecular mechanisms of action are not completely understood. Intravenously administered vidarabine has been shown to be effective in the treatment of herpes simplex encephalitis, mucocutaneous HSV infections and herpes zoster in immunocompromised patients and of neonatal HSV infections. Its use has been supplanted by intravenous acyclovir, which is more effective and easier to administer. Production of the intravenous preparation has been discontinued by the manufacturer, but vidarabine is available as an ophthalmic ointment, which is effective in the treatment of HSV keratitis.

## OTHER ANTIVIRAL DRUGS

*Lamivudine* is a pyrimidine nucleoside analogue that is used primarily in combination therapy against HIV infection (Chap. 309). It is also active againstHBVthrough inhibition of the viral DNA polymerase and has been approved for the treatment of chronic HBV infection. In one study, at doses of 100 mg/d for³1 year, lamivudine was well tolerated and resulted in suppression of HBV DNA levels, normalization of serum aminotransferase levels in most patients, and reduction of hepatic inflammation and fibrosis. Loss of hepatitis B e antigen (HBeAg) occurred in a minority of patients. Resistance to lamivudine developed in 15 to 36% of patients treated for 1 year and was associated with changes in the YMDD motif of HBV DNA polymerase. This is an important limitation of monotherapy with the drug. Studies of lamivudine as a component of combination therapy for hepatitis B are under way. Lamivudine also appears to be useful in the prevention or suppression of HBV infection associated with liver transplantation.

*Lobucavir* is a synthetic cyclobutane nucleoside analogue with activity against a broad

range of herpesviruses, HIV, andHBV. It is currently under investigation in clinical trials. Its mechanism of action is through inhibition of viral DNA synthesis. Lobucavir is initially phosphorylated by virus-induced kinases, and lobucavir triphosphate is a potent inhibitor ofHSV,CMV, and HBV DNA polymerases. Lobucavir can be administered orally or intravenously. It is excreted largely unmetabolized via the kidney and has a plasma half-life of 2 h after intravenous administration. Its oral availability is dose-dependent, ranging from 25 to 40% at doses of £200 mg and decreasing at higher doses. The preclinical toxicity profile of lobucavir appears to be similar to that of ganciclovir. However, neutropenia has been uncommonly encountered in studies in humans. Aminotransferase elevations have been documented after intravenous and (less commonly) oral administration. The most frequent adverse effects after oral administration are headache, insomnia, and gastrointestinal discomfort. In clinical trials to date, oral lobucavir has demonstrated antiviral effects in CMV- and HBV-infected patients as well as clinical benefits against HSV infections in immunocompetent patients. Short-term (1-month) oral administration of 200 mg of lobucavir bid or qid reduced serum HBV DNA levels in chronically infected patients. HBV DNA levels returned to pretreatment values when the drug was stopped, and studies of longer-term administration are under way. Lobucavir is under clinical investigation for use in HIV infection and in several herpesvirus infections.

*Pleconaril* is an investigational drug active in vitro against picornavirus replication, including over 90% of the most commonly isolated enterovirus types and 80% of rhinovirus serotypes. Its mechanism of action is through binding to a specific hydrophobic pocket in the viral capsid, which prevents attachment and/or uncoating of the virus. Pleconaril is poorly water soluble and is formulated as an oral suspension. After oral administration of 200- and 400-mg doses to adults, peak plasma concentrations are 1.1 and 2.4 ug/mL, respectively, and the terminal plasma half-life is 25 h. Pleconaril is generally well tolerated; the most frequently reported adverse effects are headache, nausea, diarrhea, and gastrointestinal discomfort, which have occurred at rates similar to those among placebo recipients. Orally administered pleconaril, given before and after experimental infection of healthy volunteers with coxsackievirus A21, reduced peak viral titers by >100-fold and decreased the subsequent rate of development of illness. Pleconaril treatment of adults with enteroviral meningitis decreased the overall duration of illness and headache and reduced the use of analgesics from that by placebo recipients. Clinical studies of pleconaril in other enterovirus-induced diseases are in progress.

## INTERFERONS

Interferons are cytokines that exhibit a broad spectrum of antiviral activities as well as immunomodulating and antiproliferative properties. TheIFNs are not available for oral administration but must be given intramuscularly, subcutaneously, or intravenously. Early studies with human leukocyte IFN demonstrated an effect in the prophylaxis of experimentally induced rhinovirus infections in humans and in the treatment ofVZVinfections in immunosuppressed patients. DNA recombinant technology has made available highly purified a,b, and g IFNs that have been evaluated in a variety of viral infections. Results of such trials have confirmed the effectiveness of intranasally administered IFN in the prophylaxis of rhinovirus infections, although its use has been associated with nasal mucosal irritation. Studies have also demonstrated a beneficial

effect of intralesionally or systemically administered IFNs on genital warts. The effect of systemic administration consists primarily of a reduction in the size of lesions, and this mode of therapy may be useful in individuals who have numerous warts that cannot easily be treated by individual intralesional injection. However, lesions frequently recur after intralesional or systemic IFN therapy is discontinued.

Interferons have undergone extensive study in the treatment of chronicHBVinfection. The administration ofIFN-a2b (5 million units daily for 16 weeks) to patients with stable chronic HBV infection resulted in loss of markers of HBV replication, such asHBeAgand HBV DNA, in 33 to 37% of cases; 10 to 20% of patients also became negative for hepatitis B surface antigen. In >80% of patients who lose HBeAg and HBV DNA markers, serum aminotransferases return to normal levels, and both short- and long-term improvements in liver histopathology have been described. Predictors of a favorable response to therapy include low pretherapy levels of HBV DNA, high pretherapy serum levels of alanine aminotransferase (ALT), a short duration of chronic HBV infection, and active liver histopathology. Poor responses are seen in immunosuppressed patients, including those with HIV infection. Adverse effects of the above dose of IFN are common and include fever, chills, myalgia, fatigue, neurotoxicity (primarily manifested as somnolence and confusion), and leukopenia. Approximately 25% of patients receiving a daily dose of 5 million units require dose reduction, but fewer than 5% require discontinuation of therapy.

SeveralIFNpreparations, including a2a,a2b, alfacon-1, and am1 (lymphoblastoid), have been studied as therapy for chronicHCVinfections. A variety of regimens have been employed, of which the most common is IFN-a2b or -a2a at 3 million units three times per week for 12 months. A complete biochemical response, defined as a return to normal serumALTvalues at the end of treatment, has been documented in ~54% of patients. In addition, liver biopsies have shown decreases in lobular and periportal inflammation. However, relapse has occurred in approximately half of all cases upon discontinuation of therapy, so that sustained responses were documented in 28% of cases. The addition of oral ribavirin to IFN-a2b -- either as initial therapy or after failure of interferon therapy alone -- resulted in significantly higher rates of sustained response (40 to 50%) than were obtained with monotherapy. Prognostic factors for a favorable response include an age of<45 years, a short duration of disease, low levels of HCV RNA, and infection with HCV genotypes other than 1. IFN alfacon, a synthetic "consensus" a interferon, appears to produce response rates similar to those elicited by IFN-a2a or -a2b and has recently been approved in the United States for the treatment of chronic hepatitis C.

Treatment of chronic hepatitis D withIFN-aapparently requires higher doses (5 million units daily or 10 million units three times per week) and is less effective than treatment of chronic hepatitis B or C. After 12 months of therapy, biochemical and virologic responses were detected in ³50% of patients, but few responses were sustained once therapy was stopped.

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Back to Table of Contents

## SECTION 12 -DNA VIRUSES

# 182. HERPES SIMPLEX VIRUSES - *Lawrence Corey*

## DEFINITION

Herpes simplex viruses (HSV-1, HSV-2; *Herpesvirus hominis*) produce a variety of infections involving mucocutaneous surfaces, the central nervous system (CNS), and -- on occasion -- visceral organs. The advent of effective chemotherapy for HSV infections has made prompt recognition of these syndromes even more clinically important than in the past.

## ETIOLOGIC AGENT

The genome ofHSV is a linear, double-stranded DNA molecule (molecular weight, ~100´$10_6$) that encodes more than 75 gene products. The genomic structures of the two HSV subtypes are similar, and the overall sequence homology between HSV-1 and HSV-2 is ~50%. The homologous sequences are distributed over the entire genome map, and most of the polypeptides specified by one viral type are antigenically related to polypeptides of the other viral type. Many type-specific regions unique to HSV-1 and HSV-2 proteins do exist, however, and a number of them appear to be important in host immunity. These type-specific regions have been used to develop serologic assays that distinguish between the two viral subtypes. Restriction endonuclease analysis of viral DNA can be used to distinguish between the two subtypes and among strains of each subtype. The variability of nucleotide sequences from clinical strains of HSV-1 and HSV-2 is such that HSV isolates obtained from two individuals can be differentiated by restriction enzyme patterns unless the isolates are from epidemiologically related sources, such as sexual partners, mother-infant pairs, or persons involved in a common-source outbreak.

The viral genome is packaged in a regular icosahedral protein shell (capsid) composed of 162 capsomers. The outer covering of the virus is a lipid-containing membrane (envelope) derived from modified cell membrane and acquired as the DNA-containing capsid buds through the inner nuclear membrane of the host cell. Between the capsid and lipid bilayer of the envelope is the tegument. Viral replication has both nuclear and cytoplasmic phases. The initial steps of replication include attachment, fusion between the viral envelope and the cell membrane to liberate the nucleocapsid into the cytoplasm of the cell, and disassembly of the nucleocapsid to release the viral DNA. Replication ofHSV is highly regulated. After fusion of the virion envelope with the host cell membrane, several viral proteins are released from the HSV virion. Some shut off host protein synthesis (by increasing cellular RNA degradation), while others "turn on" transcription of early genes of HSV replication. These early gene products, designated *a genes*, are required for synthesis of the subsequent polypeptide group, theb polypeptides, many of which are regulatory proteins and enzymes required for DNA replication. Most current antiviral drugs interfere with b proteins, such as the viral DNA polymerase enzyme. The third (g) class of HSV genes requires viral DNA replication for expression and constitutes most of the structural proteins specified by the virus.

After replication of the viral genome and synthesis of structural proteins, nucleocapsids

are assembled in the nucleus of the cell. Envelopment occurs as the nucleocapsids bud through the inner nuclear membrane into the perinuclear space. In some cells, viral replication in the nucleus forms two types of inclusion bodies: type A basophilic Feulgen-positive bodies that contain viral DNA and an eosinophilic inclusion body that is devoid of viral nucleic acid or protein and represents a "scar" of viral infection. Virions are then transported via the endoplasmic reticulum and the Golgi apparatus to the cell surface.

HSVinfection of some neuronal cells does not result in cell death. Instead, viral genomes are maintained by the cell in a repressed state compatible with survival and normal activities of the cell, a condition called *latency*. Latency is associated with transcription of only a limited number of virus-encoded proteins. Subsequently, the viral genome may become activated, resulting in the normal pattern of regulated viral gene expression, replication, and release of HSV. The release of virus from the neuron and its subsequent entry into epithelial cells result in viral replication. This process is termed *reactivation*. Whereas infectious virus rarely can be recovered from sensory or autonomic nervous system ganglia dissected from cadavers, maintenance and growth of the neural cells in tissue culture result in production of infectious virions (*explantation*) and in subsequent permissive infection of susceptible cells (*cocultivation*). The fact that HSV replication was first detected in neurons during reactivation in vitro suggested that the neuron harbors the latent virus in vivo. Viral DNA and RNA have since been found in neural tissue at times when infectious virus cannot be isolated. Two RNA "latency-associated" transcripts that overlap the immediate early (a) gene products, called ICP-O, are found in abundance in the nuclei of latently infected neurons. These latency-associated transcripts code proteins in an antisense direction. Deletion mutants of this region that can become latent have been made. However, the efficiency of their later reactivation is reduced; thus, the antisense transcripts may play a role in maintaining rather than in establishing latency. At present, the molecular mechanisms of the latency of HSV-1 and HSV-2 are not well understood, and strategies to interrupt latency or to maintain molecular latency in neurons are not available.

**PATHOGENESIS**

Exposure to HSVat mucosal surfaces or abraded skin sites permits entry of the virus and initiation of its replication in cells of the epidermis and dermis. Investigators have identified several cell receptors that are ligands for HSV attachment proteins. Studies to define how these receptors influence viral replication and pathogenesis are under way. Initial HSV infection is often subclinical -- i.e., without clinically apparent lesions. Both clinical acquisition and subclinical acquisition are associated with sufficient viral replication to permit infection of either sensory or autonomic nerve endings. On entry into the neuronal cell, the virus -- or, more likely, the nucleocapsid -- is transported intraaxonally to the nerve cell bodies in ganglia. In humans, the interval from inoculation of virus in peripheral tissue to spread to the ganglia is unknown. During the initial phase of infection, viral replication occurs in ganglia and contiguous neural tissue. Virus then spreads to other mucosal skin surfaces through centrifugal migration of infectious virions via peripheral sensory nerves. This mode of spread helps explain the large surface area involved, the high frequency of new lesions distant from the initial crop of vesicles that is characteristic in patients with primary genital or oral-labial HSV infection, and the recovery of virus from neural tissue distant from neurons innervating the

inoculation site. Contiguous spread of locally inoculated virus also may take place and allow further mucosal extension of disease.

After the resolution of primary disease, infectiousHSV can no longer be recovered in the ganglia. However, viral DNA can be found in 10 to 50% of ganglion cells in the anatomic region of the initial infection. Only ~1% of such cells express latency-associated transcripts of RNA detectable by current techniques. The mechanisms controlling the reactivation of HSV infection are unknown. Alterations in cellular transcripts that "maintain" latency are suspected, and several cellular protein kinases are under investigation. Experimentally, ultraviolet light, systemic and local immunosuppression, and trauma to the skin or ganglia are associated with reactivation.

Analysis of the DNA from sequentially isolated strains ofHSV or from isolates from multiple infected ganglia in any one individual has revealed identical restriction endonuclease patterns in most persons. Occasionally (most frequently in immunocompromised persons), multiple strains of the same viral subtype are detected in one individual. This finding suggests that exogenous infection with different strains of the same subtype is possible although very uncommon.

**IMMUNITY**

Host responses to infection withHSVinfluence the acquisition of disease, the severity of infection, resistance to the development of latency, the maintenance of latency, and the frequency of recurrences. Both antibody-mediated and cell-mediated reactions are clinically important. Immunocompromised patients with defects in cell-mediated immunity experience more severe and more extensive HSV infections than those with deficits in humoral immunity, such as agammaglobulinemia. Experimental ablation of lymphocytes indicates that T cells play a major role in preventing lethal disseminated disease, although antibodies help reduce virus titers in neural tissue. Some of the clinical manifestations of HSV disease appear to be related to the host immune response (e.g., stromal opacities associated with recurrent herpetic keratitis). The surface viral glycoproteins have been shown to be antigens recognized by antibodies mediating neutralization and immune-mediated cytolysis (antibody-dependent cell-mediated cytotoxicity). Monoclonal antibodies specific for each of the known viral glycoproteins have, in experimental infections, conferred protection against subsequent neurologic disease or ganglionic latency. However, the use of subunit glycoprotein vaccines in humans has not been successful in reducing acquisition of infection, despite high titers of type-specific antibodies. Multiple cell populations, including natural killer cells, macrophages, a variety of T lymphocytes, and lymphokines generated by these cells, play a role in host defenses against HSV infections. In animals, passive transfer of primed lymphocytes confers protection from subsequent challenge. Maximum protection usually requires the activation of multiple T cell subpopulations, including cytotoxic T cells and T cells responsible for delayed hypersensitivity. The latter cells may confer protection by the antigen-stimulated release of lymphokines (e.g., interferons), which may have a direct antiviral effect and may activate and enhance a variety of specific and nonspecific effector cells. Increasing evidence suggests that HSV-specific CD8+ T cell responses are critical for clearance of virus from lesions. In addition, immunosuppressed patients with frequent and prolonged HSV lesions have fewer functional CD8+ T cells directed at HSV. The HSV virion contains a gene called unique

long gene no. 12 (UL-12) that can bind to the cellular transporter-activating protein TAP-1 and reduce the ability of this protein to bind HSV peptides to HLA class I, thereby reducing recognition of viral proteins by cytotoxic T cells of the host. This effect can be overcome by the addition of interferon g, but this requires 24 to 48 h; thus, the virus has time to replicate and invade other host cells. Prior HSV-1 infection does not appear to reduce the frequency of acquisition of HSV-2 as measured by seroconversion. However, persons with prior HSV-1 infection who acquire HSV-2 appear to have a greater frequency of subclinical acquisition. These data suggest that type-specific immune responses are central to the control of HSV infection.

**EPIDEMIOLOGY**

Seroepidemiologic studies have documentedHSVinfections worldwide. Much of the humoral immune response to HSV is to type-common antigenic determinants. Serologic assays with whole-virus antigen preparations, such as complement fixation, neutralization, indirect immunofluorescence, passive hemagglutination, radioimmunoassay, and enzyme-linked immunosorbent assay, do not reliably distinguish between the two viral subtypes. Such assays are useful for differentiating uninfected (seronegative) persons from those with past HSV-1 or HSV-2 infection, but they do not reliably distinguish between the two subtypes. Serologic assays that identify antibodies to type-specific surface proteins of the two subtypes have been developed. These assays, which are based on the demonstration of antibodies to type-specific epitopes of the virus, can reliably distinguish between the human antibody responses to HSV-1 and HSV-2. The most commonly used assays are those that measure antibodies to glycoprotein G of HSV-1 (gG1) and HSV-2 (gG2). A western blot assay that can detect several HSV type-specific proteins can also be used.

Infection withHSV-1 is acquired more frequently and earlier than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. In populations of low socioeconomic status, most persons acquire HSV-1 infection before the third decade of life.

Antibodies toHSV-2 are not detected routinely until puberty. Antibody prevalence rates correlate with past sexual activity and vary greatly among different population groups. Serosurveys indicate that nearly 22% of the United States population has antibodies to HSV-2 -- a 30% increase in the past 12 years. In most routine obstetric and family planning clinics, 25% of women have HSV-2 antibodies, although only 10% report a history of genital lesions. As many as 50% of heterosexual adults attending sexually transmitted disease clinics have antibodies to HSV-2. Antibody prevalence rates average about 5% higher among women than among men. Several studies suggest that much of this "asymptomatic" infection is largely unrecognized in that when "asymptomatic" seropositive persons are shown pictures of genital lesions,>60% subsequently identify episodes of symptomatic reactivation. Most important, these asymptomatic seropositive persons with reactivation shed virus on mucosal surfaces as frequently as those with symptomatic disease. The large reservoir of unidentified carriers of HSV-2 and the frequent asymptomatic reactivation of virus from the genital tract have fostered the continued spread of genital herpes throughout the world. HSV-2 infection is an independent risk factor for the acquisition and transmission of infection with HIV type 1. Among coinfected persons, HIV-1 virions can be shed from herpetic

lesions of the genital region. This shedding may facilitate the spread of HIV through sexual contact.

HSVinfections occur throughout the year. The incubation period ranges from 1 to 26 days (median, 6 to 8 days). Transmission can result from contact with persons with active ulcerative lesions or with persons without clinical manifestations of infection who are shedding HSV or on whose mucosal surfaces the virus is replicating. Studies using the polymerase chain reaction (PCR) have shown that HSV reactivation on mucosal surfaces is much more frequent than previously recognized. Among immunocompetent adults, HSV-2 can be isolated from the genital tract on 2 to 3% of days, and HSV DNA can be detected on 20 to 30% of days. Corresponding figures for HSV-1 in oral secretions are similar. Shedding rates are highest during the initial years of acquisition and may be as high as 30 to 50% of days during this period. Immunosuppressed patients shed HSV on mucosal sites at even higher frequency (20 to 50% of days). Daily antiviral chemotherapy can markedly reduce shedding rates. These data indicate that potential exposure to HSV from sexual or other close contact (kissing, sharing of glasses or silverware) is more common than has been thought. These shedding-rate data are consistent with the high seroprevalence of HSV infections worldwide.

## CLINICAL SPECTRUM

HSVhas been isolated from nearly all visceral or mucocutaneous sites. The clinical manifestations and course of HSV infection depend on the anatomic site involved, the age and immune status of the host, and the antigenic type of the virus. Primary HSV infections (i.e., first infections with either HSV-1 or HSV-2 in which the host lacks HSV antibodies in acute-phase serum) are frequently accompanied by systemic signs and symptoms, involve both mucosal and extramucosal sites, and have a longer duration of symptoms, a longer duration of virus isolation from lesions, and a higher rate of complications than recurrent episodes of disease. Both viral subtypes can cause genital and oral-facial infections, and the infections caused by the two subtypes are clinically indistinguishable. However, the frequency of reactivation of infection is influenced by anatomic site and virus type. Genital HSV-2 infection is twice as likely to reactivate and recurs 8 to 10 times more frequently than genital HSV-1 infection. Conversely, oral-labial HSV-1 infection recurs more frequently than oral-labial HSV-2 infection. Asymptomatic shedding rates follow the same pattern.

**Oral-Facial Infections** Gingivostomatitis (Fig. 182-CD1) and pharyngitis are the most frequent clinical manifestations of first-episodeHSV-1 infection, while recurrent herpes labialis (Fig. 182-CD2) is the most frequent clinical manifestation of reactivation HSV infection. HSV pharyngitis and gingivostomatitis usually result from primary infection and are most commonly seen in children and young adults. Clinical symptoms and signs, which include fever, malaise, myalgias, inability to eat, irritability, and cervical adenopathy, may last from 3 to 14 days. Lesions may involve the hard and soft palate, gingiva, tongue, lip, and facial area. HSV-1 or HSV-2 infection of the pharynx usually results in exudative or ulcerative lesions of the posterior pharynx and/or tonsillar pillars. Lesions of the tongue, buccal mucosa, or gingiva may occur later in the course in one-third of cases. Fever lasting from 2 to 7 days and cervical adenopathy are common. It can be difficult to differentiate HSV pharyngitis clinically from bacterial pharyngitis, *Mycoplasma pneumoniae* infections, and pharyngeal ulcerations of noninfectious

etiologies (e.g., Stevens-Johnson syndrome). No substantial evidence suggests that reactivation oral-labial HSV infection is associated with symptomatic recurrent pharyngitis.

Reactivation of HSVfrom the trigeminal ganglia may be associated with asymptomatic virus excretion in the saliva, development of intraoral mucosal ulcerations, or herpetic ulcerations on the vermilion border of the lip or external facial skin. About 50 to 70% of seropositive patients undergoing trigeminal nerve root decompression and 10 to 15% of those undergoing dental extraction develop oral-labial HSV infection a median of 3 days after these procedures.

In immunosuppressed patients, infection may extend into mucosal and deep cutaneous layers (Fig. 182-CD3). Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result. The lesions ofHSVmucositis are clinically similar to mucosal lesions caused by cytotoxic drug therapy, trauma, or fungal or bacterial infections. Persistent ulcerative HSV infections are among the most common infections in patients with AIDS. HSV and *Candida* infections often occur concurrently. Systemic antiviral therapy speeds the rate of healing and relieves the pain of mucosal HSV infections in immunosuppressed patients. The frequency of HSV reactivation during the early phases of transplantation or induction chemotherapy is high (50 to 90%), and prophylactic systemic antivirals such as intravenous acyclovir or penciclovir are used to reduce reactivation rates. Patients with atopic eczema also may develop severe oral-facial HSV infections (eczema herpeticum), which may rapidly come to involve extensive areas of skin and occasionally disseminate to visceral organs. Extensive eczema herpeticum has resolved promptly with the administration of intravenous acyclovir. Erythema multiforme (EM) also may be associated with HSV infections (Plate IIE-67); some evidence suggests that HSV infection is the precipitating event in ~75% of cases of cutaneous EM. HSV antigen has been demonstrated both in circulatory immune complexes and in skin lesion biopsy samples from these patients. Patients with severe HSV-associated EM are candidates for chronic suppressive oral antiviral therapy.

HSV-1 has been implicated in the etiology of Bell's palsy (flaccid paralysis of the mandibular portion of the facial nerve). Whether antiviral chemotherapy can alter the clinical course and complications of this infection is unclear.

**Genital Infections** First-episode primary genital herpes is characterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms. Widely spaced bilateral lesions of the external genitalia are characteristic. Lesions may be present in varying stages, including vesicles, pustules, or painful erythematous ulcers. The cervix and urethra are involved in>80% of women with first-episode infections. First episodes of genital herpes in patients who have had priorHSV-1 infection are associated with less frequent systemic symptoms and faster healing than primary genital herpes. The clinical courses of acute first-episode genital herpes among patients with HSV-1 and HSV-2 infections are similar. However, the recurrence rates of genital disease (Figs. 182-CD4,182-CD5,182-CD6) differ with the viral subtype: the 12-month recurrence rates among patients with first-episode HSV-2 and HSV-1 infections are ~90% and ~55%, respectively (median number of recurrences, 4 and <1, respectively). Recurrence rates for genital HSV-2 infections vary greatly among individuals and over

time within the same individual. HSV has been isolated from the urethra and urine of men and women without external genital lesions. A clear mucoid discharge and dysuria are characteristics of symptomatic HSV urethritis. HSV has been isolated from the urethra of 5% of women with the dysuria-frequency syndrome. Occasionally, HSV genital tract disease is manifested by endometritis and salpingitis in women and by prostatitis in men. About 15% of cases of HSV-2 acquisition are associated with these nonlesional clinical syndromes, such as aseptic meningitis, cervicitis, or urethritis.

BothHSV-1 and HSV-2 can cause symptomatic or asymptomatic rectal and perianal infections. HSV proctitis is usually associated with rectal intercourse. However, subclinical perianal shedding of HSV is detected both in heterosexual men and in women who report no rectal intercourse. This phenomenon is due to the establishment of latency in the sacral dermatome from prior genital tract infection, with subsequent reactivation in epithelial cells in the perianal region. Such reactivations are often subclinical. Symptoms of HSV proctitis include anorectal pain, anorectal discharge, tenesmus, and constipation. Sigmoidoscopy reveals ulcerative lesions of the distal 10 cm of the rectal mucosa. Rectal biopsies show mucosal ulceration, necrosis, polymorphonuclear and lymphocytic infiltration of the lamina propria, and (in occasional cases) multinucleated intranuclear inclusion-bearing cells. Perianal herpetic lesions are also found in immunosuppressed patients receiving cytotoxic therapy. Extensive perianal herpetic lesions and/or HSV proctitis is common among patients with HIV infection.

**Herpetic Whitlow (Fig. 182-CD7)** Herpetic whitlow -- HSVinfection of the finger -- may occur as a complication of primary oral or genital herpes by inoculation of virus through a break in the epidermal surface or by direct introduction of virus into the hand through occupational or some other type of exposure. Clinical signs and symptoms include the abrupt onset of edema, erythema, and localized tenderness of the infected finger. Vesicular or pustular lesions of the fingertip that are indistinguishable from lesions of pyogenic bacterial infection are seen. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common. The infection may recur. Prompt diagnosis (to avoid unnecessary and potentially exacerbating surgical therapy and/or transmission) is essential. Antiviral chemotherapy (to speed the healing of the process) is usually recommended (see below).

**Herpes Gladiatorum** HSV may infect almost any area of skin. Mucocutaneous HSV infections of the thorax, ears, face, and hands have been described among wrestlers. Transmission of these infections is facilitated by trauma to the skin sustained during wrestling. Prompt diagnosis and therapy are required to contain the spread of this infection.

**Eye Infections** HSVinfection of the eye is the most frequent cause of corneal blindness in the United States. HSV keratitis presents with an acute onset of pain, blurring of vision, chemosis, conjunctivitis, and characteristic dendritic lesions of the cornea. Use of topical glucocorticoids may exacerbate symptoms and lead to involvement of deep structures of the eye. Debridement, topical antiviral treatment, and/or interferon therapy hastens healing. However, recurrences are common, and the deeper structures of the eye may sustain immunopathologic injury. Stromal keratitis due to HSV appears to be related to T cell-dependent destruction of deep corneal tissue. An HSV-1 epitope that is

autoreactive with T cell-targeting corneal antigens has been postulated to be a factor in this infection. Chorioretinitis, usually a manifestation of disseminated HSV infection, may occur in neonates or in patients with HIV infection. HSV and varicella-zoster virus can cause acute necrotizing retinitis as an uncommon but severe manifestation.

**Central and Peripheral Nervous System Infections** HSVaccounts for 10 to 20% of all cases of sporadic viral encephalitis in the United States. The estimated incidence is about 2.3 cases per million persons per year. Cases are distributed throughout the year, and the age distribution appears to be biphasic, with peaks at 5 to 30 and >50 years of age. Subtype 1 virus causes >95% of cases of HSV encephalitis.

The pathogenesis ofHSVencephalitis varies. In children and young adults, primary HSV infection may result in encephalitis; presumably, exogenously acquired virus enters theCNS by neurotropic spread from the periphery via the olfactory bulb. However, most adults with HSV encephalitis have clinical or serologic evidence of mucocutaneous HSV-1 infection before the onset of the CNS symptoms. In ~25% of the cases examined, the HSV-1 strains from the oropharynx and brain tissue of the same patient differ; thus some cases may result from reinfection with another strain of HSV-1 that reaches the CNS. Two theories have been proposed to explain the development of actively replicating HSV in localized areas of the CNS in persons whose ganglionic and CNS isolates are similar. Reactivation of latent HSV-1 infection in trigeminal or autonomic nerve roots may be associated with extension of virus into the CNS via nerves innervating the middle cranial fossa. HSV DNA has been demonstrated by DNA hybridization in brain tissue obtained at autopsy -- even from healthy adults. Thus, reactivation of long-standing latent CNS infection may be another mechanism for the development of HSV encephalitis.

The clinical hallmark ofHSVencephalitis has been the acute onset of fever and focal neurologic (especially temporal-lobe) symptoms. Clinical differentiation of HSV encephalitis from other viral encephalitides, focal infections, or noninfectious processes is difficult. The most sensitive noninvasive method for early diagnosis of HSV encephalitis is the demonstration of HSV DNA in cerebrospinal fluid (CSF) byPCR. Although titers of CSF and serum antibodies to HSV increase in most cases of HSV encephalitis, they rarely do so earlier than 10 days into the illness and therefore, while useful retrospectively, are generally not helpful in establishing an early clinical diagnosis. Demonstration of HSV antigen, HSV DNA, or HSV replication in brain tissue obtained by biopsy is highly sensitive and has a low complication rate; examination of such tissue also provides the best opportunity to identify alternative, potentially treatable causes of encephalitis. Antiviral chemotherapy reduces the rate of death from HSV encephalitis. Intravenous acyclovir is more effective than vidarabine. Even with therapy, however, neurologic sequelae are frequent, especially in persons over 35 years of age. Most authorities recommend the administration of intravenous acyclovir to patients with presumed HSV encephalitis until the diagnosis is confirmed or an alternative diagnosis is made.

HSVhas been isolated from theCSF of 0.5 to 3% of patients presenting to the hospital with aseptic meningitis. HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute, self-limited disease manifested by headache, fever, and mild photophobia and lasting from 2 to 7 days. Lymphocytic pleocytosis in the

CSF is characteristic. Neurologic sequelae of HSV meningitis are rare. HSV is the most commonly identified cause of recurrent lymphocytic meningitis (Mollaret's meningitis). Demonstration of HSV antibodies in CSF or persistence of HSV DNA in CSF can establish the diagnosis. Daily administration of antiviral therapy aimed at reducing the likelihood of clinical HSV reactivation has been successful in such cases.

Autonomic nervous system dysfunction, especially of the sacral region, has been reported in association with bothHSV and varicella-zoster virus infections. Numbness, tingling of the buttocks or perineal areas, urinary retention, constipation,CSFpleocytosis, and (in males) impotence may occur. Symptoms appear to resolve slowly over days to weeks. Occasionally, hypesthesia and/or weakness of the lower extremities may persist for many months. Rarely, transverse myelitis manifested by a rapidly progressive symmetric paralysis of the lower extremities or a Guillain-Barre syndrome may follow HSV infection. Similarly, peripheral nervous system involvement (Bell's palsy) or cranial polyneuritis also may be related to reactivation of HSV-1 infection. Transitory hypesthesia of the area of skin innervated by the trigeminal nerve and vestibular system dysfunction as measured by electronystagmography are the predominant signs of disease. Studies to determine whether antiviral chemotherapy may abort these signs or reduce their frequency and severity are unavailable.

**Visceral Infections** HSVinfection of visceral organs usually results from viremia, and multiple-organ involvement is common. Occasionally, however, the clinical manifestations of HSV infection involve only the esophagus, lung, or liver. HSV esophagitis may result from direct extension of oral-pharyngeal HSV infection into the esophagus or may occur de novo by reactivation and spread of HSV to the esophageal mucosa via the vagus nerve. The predominant symptoms of HSV esophagitis are odynophagia, dysphagia, substernal pain, and weight loss. There are multiple oval ulcerations on an erythematous base with or without a patchy white pseudomembrane. The distal esophagus is most commonly involved. With extensive disease, diffuse friability may spread to the entire esophagus. Neither endoscopic nor barium examination can differentiate HSV esophagitis from *Candida* esophagitis or from esophageal ulcerations due to thermal injury, radiation, or corrosives. Endoscopically obtained secretions for cytologic examination and culture provide the most useful material for diagnosis. Systemic antiviral chemotherapy usually reduces symptoms and heals esophageal ulcerations.

HSVpneumonitis is uncommon except in severely immunosuppressed patients and may result from extension of herpetic tracheobronchitis into lung parenchyma. Focal necrotizing pneumonitis usually ensues. Hematogenous dissemination of virus from sites of oral or genital mucocutaneous disease also may occur and produce bilateral interstitial pneumonitis. Bacterial, fungal, and parasitic pathogens are commonly present in HSV pneumonitis. The mortality rate from untreated HSV pneumonia in immunosuppressed patients is high (>80%). HSV has also been isolated from the lower respiratory tract of persons with adult respiratory distress syndrome (ARDS). However, the relationship between the isolation of HSV and the pathogenesis of ARDS is unclear.

HSVis an uncommon cause of hepatitis in immunocompetent patients. HSV infection of the liver is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (<4000 white blood cells per microliter).

Disseminated intravascular coagulation also may develop.

Other reported complications ofHSVinfection include monarticular arthritis, adrenal necrosis, idiopathic thrombocytopenia, and glomerulonephritis. Disseminated HSV infection (Fig. 182-CD8) in immunocompetent patients is rare. In immunocompromised, burned, or malnourished patients, HSV occasionally disseminates to other visceral organs, such as the adrenal glands, pancreas, small and large intestines, and bone marrow. Rarely, primary HSV infection in pregnancy disseminates and may be associated with the death of both mother and fetus. This uncommon event is usually related to the acquisition of primary infection in the third trimester.

**Neonatal HSV Infection** Neonates (infants younger than 6 weeks) have the highest frequency of visceral and/orCNSinfection of anyHSV-infected patient population. Without therapy, the overall rate of death from neonatal herpes is 65%; fewer than 10% of neonates with CNS infection develop normally. Although skin lesions are the most commonly recognized features of disease, many infants do not develop lesions until well into the course of disease. Neonatal infection is usually acquired perinatally from contact with infected genital secretions at the time of delivery. Congenitally infected infants have been reported. In most series, 30% of neonatal HSV infections are due to HSV-1 and 70% to HSV-2. The risk of developing neonatal HSV infection is 10 times higher for an infant born to a mother who has recently acquired HSV than for other infants. Guidelines to evaluate routine serologic testing for HSV in pregnancy are being drafted and will serve as a basis on which to counsel "susceptible" (HSV-2-uninfected) women regarding the dangers of unprotected coitus and HSV-2 infection near term. Neonatal HSV-1 infections may also be acquired through postnatal contact with immediate family members who have symptomatic or asymptomatic oral-labial HSV-1 infection or through nosocomial transmission within the hospital. Antiviral chemotherapy has reduced the rate of death from neonatal herpes to 25%. However, the rate of morbidity, especially in infants with HSV-2 infection involving the CNS, is still very high.

## DIAGNOSIS

Both clinical and laboratory criteria are useful for establishing the diagnosis ofHSVinfections. A clinical diagnosis can be made accurately when characteristic multiple vesicular lesions on an erythematous base are present. However, it is increasingly being recognized that herpetic ulcerations may clinically resemble skin ulcerations of other etiologies. Mucosal HSV infections may also present as urethritis or pharyngitis without cutaneous lesions. Thus, laboratory studies to confirm the diagnosis and to guide therapy are recommended. Staining of scrapings from the base of the lesions with Wright's, Giemsa's (Tzanck preparation; Fig. 182-CD9), or Papanicolaou's stain demonstrates characteristic giant cells or intranuclear inclusions of herpesvirus infection. These cytologic techniques are often useful as quick office procedures to confirm the diagnosis. Limitations of the cytologic method are that it does not differentiate between HSV and varicella-zoster virus infections, that it is relatively insensitive, and that the correct identification of giant cells requires experience.

HSVinfection is best confirmed in the laboratory by isolation of virus in tissue culture or by demonstration of HSV antigens or DNA in scrapings from lesions. HSV causes a discernible cytopathic effect in a variety of cell culture systems, and most specimens