The toll of tetanus. The bacterial genus *Clostridium* contains many pathogenic species, including the species responsible for tetanus (*C. tetani*). Sir Charles Bell’s portrait (c. 1821) of a soldier wounded in the Peninsular War in Spain shows the suffering from generalized tetanus.
Chapter 39 Human Diseases Caused by Bacteria

The food-borne and waterborne bacterial diseases are contracted when contaminated food or water is ingested. These diseases are essentially of two kinds: intoxications and intoxications. An infection occurs when a pathogen enters the gastrointestinal tract and multiplies. Examples include Campylobacter jejuni, salmonellosis, listeriosis, shigellosis, traveler’s diarrhea, Escherichia coli infections, and typhoid fever. An intoxication occurs because of the ingestion of a toxin produced outside the body. Examples include botulism, cholera, and staphylococcal food poisoning.

Some microbial diseases and their effects cannot be categorized under a specific mode of transmission. Two important examples are sepsis and septic shock. Gram-positive bacteria, fungi, and endotoxin-containing gram-negative bacteria can cause skin diseases, including cellulitis, erysipelas, and scarlet fever, or systemic diseases such as meningitis, glomerulonephritis, and rheumatic fever.

Most of the airborne diseases caused by bacteria involve the respiratory system. Other airborne bacteria can cause skin diseases, including cellulitis, erysipelas, and scarlet fever, or systemic diseases such as meningitis, glomerulonephritis, and rheumatic fever.

Although arthropod-borne bacterial diseases are generally rare, they are of interest either historically (plague) or because they have been newly introduced into humans (Lyme disease). Most of the rickettsial diseases are arthropod-borne. The rickettsias found in the United States can be divided into the typhus group (epidemic typhus caused by R. prowazekii and murine typhus caused by R. typhi) and the spotted fever group. Epidemic typhus and murine typhus, with Q fever (caused by Coxiella burnetii) being an exception because it forms endosporelike structures and does not have to use an insect vector as with other rickettsias.

Most of the direct contact bacterial diseases involve the skin, mucous membranes, or underlying tissues. Examples include anthrax, bacterial vaginosis, cat-scratch disease, chancroid, gas gangrene, leprosy, peptic ulcer disease and gastritis, staphylococcal diseases, and syphilis. Other airborne bacteria can become disseminated throughout specific regions of the body—for example, gonorrhea, staphylococcal diseases, syphilis, tetanus, and tularaemia. Three chlamydial species cause direct contact disease: Chlamydia pneumoniae causes chlamydial pneumonia; Chlamydia trachomatis causes inclusion conjunctivitis, lymphogranuloma venereum, nongonococcal urethritis, and trachoma; and C. psittaci causes psittacosis. Three species of mycoplasmas are human pathogens: Mycoplasma hominis and Ureaplasma urealyticum cause genitourinary tract disease, whereas M. pneumoniae is a major cause of acute respiratory disease and pneumonia.

The food-borne and waterborne bacterial diseases are contracted when contaminated food or water is ingested. These diseases are essentially of two types: infections and intoxications. An infection occurs when a pathogen enters the gastrointestinal tract and multiplies. Examples include Campylobacter jejuni, salmonellosis, listeriosis, shigellosis, traveler’s diarrhea, Escherichia coli infections, and typhoid fever. An intoxication occurs because of the ingestion of a toxin produced outside the body. Examples include botulism, cholera, and staphylococcal food poisoning.

Some microbial diseases and their effects cannot be categorized under a specific mode of transmission. Two important examples are sepsis and septic shock. Gram-positive bacteria, fungi, and endotoxin-containing gram-negative bacteria can initiate the pathogenic cascade of sepsis leading to septic shock.

Several bacterial odontopathogens are responsible for the most common bacterial diseases in humans—tooth decay and periodontal disease. Both are the result of plaque formation and the production of lactic and acetic acids by the odontopathogens.

Soldiers have rarely won wars. They more often mop up after the barrage of epidemics. And typhus, with its brothers and sisters—plague, cholera, typhoid, dysentery—has had more campaigns than Caesar, Hannibal, Napoleon, and all the . . . generals of history. The epidemics get the blame for the defeat, the generals the credit for victory. It ought to be the other way around . . . .
—Hans Zinsser

The first four parts of this textbook cover the general biology of bacteria. Chapters 19 through 24 specifically review bacterial morphology and taxonomy. Chapter 39 continues the coverage of bacteria by discussing some of the more important gram-positive and gram-negative bacteria, chlamydiae, mycoplasmas, and rickettsias that are pathogenic to humans. The microorganisms involved in dental infections are also described.

Of all the known bacterial species, only a few are pathogenic to humans. Some human bacterial diseases have been only recently recognized (table 39.1); others have been known since antiquity. In the following sections the more important disease-causing bacteria are discussed according to their mode of acquisition/transmission.

### 39.1 Airborne Diseases

Most airborne diseases caused by bacteria involve the respiratory system. Other airborne bacteria can cause skin diseases. Some of the better known of these diseases are now discussed.

#### Diphtheria

Diphtheria [Greek diphthera, membrane, and ia, condition] is an acute contagious disease caused by the gram-positive Corynebacterium diphtheriae (see figure 24.8). *C. diphtheriae* is well adapted to airborne transmission by way of nasopharyngeal secretions and is very resistant to drying. Diphtheria mainly affects poor people living in crowded conditions. Once within the respiratory system, bacteria that carry the prophage $\beta$ containing the tox gene (see section 17.5) produce diphtheria toxin, an exotoxin that causes an inflammatory response and the formation of a grayish pseudomembrane on the respiratory mucosa (figure 39.1). The pseudomembrane consists of dead host cells and cells of *C. diphtheriae*. The exotoxin is also absorbed into the circulatory system and distributed throughout the body,
where it may cause destruction of cardiac, kidney, and nervous tissues by inhibiting protein synthesis (see table 34.6 and figure 34.5).

Typical symptoms of diphtheria include a thick mucopurulent (containing both mucus and pus) nasal discharge, fever, and cough. Diagnosis is made by observation of the pseudomembrane in the throat and by bacterial culture. Diphtheria antitoxin is given to neutralize any unabsorbed exotoxin in the patient’s tissues; penicillin and erythromycin are used to treat the infection. Prevention is by active immunization with the DPT (diphtheria-pertussis-tetanus) vaccine (see table 33.1).

C. diphtheriae can also infect the skin, usually at a wound or skin lesion, causing a slow-healing ulceration termed cutaneous diphtheria. Most cases involve people over 30 years of age who have a weakened immunity to the diphtheria toxin and live in tropical areas.

Fewer than 100 diphtheria cases are reported annually in the United States, and most occur in nonimmunized individuals. Since 1990, a massive and expanding epidemic of diphtheria has been underway in 14 of the 15 new independent states of the former Soviet Union with approximately 50,000 new cases reported each year.

Legionnaires’ Disease and Pontiac Fever

In 1976 the term Legionnaires’ disease, or legionellosis, was coined to describe an outbreak of pneumonia that occurred at the Pennsylvania State American Legion Convention in Philadelphia. The bacterium responsible for the outbreak was described as Legionella pneumophila, a nutritionally fastidious aerobic gram-negative rod (figure 39.2). It is now known that this bacterium is part of the natural microbial community of soil and aquatic ecosystems, and it has been found in large numbers in air-conditioning systems and shower stalls.

An increasing body of evidence suggests that environmental protozoa are the most important factor for the survival and growth of Legionella in nature (see p. 608). A variety of free-living amoebae and ciliated protozoa that contain Legionella spp. have been isolated from water sites suspected as sources of Legionella infections. Legionella spp. multiply intracellularly within the amoebae, just as they do within human monocytes and macrophages. This might explain why there is no human-to-human spread of legionellosis.

Infection with L. pneumophila results from the airborne spread of bacteria from an environmental reservoir to the human respiratory system. Males over 50 years of age most commonly contract the disease, especially if their immune system is compromised by heavy smoking, alcoholism, or chronic illness. The bacteria reside within the phagosomes of alveolar macrophages, where they multiply and produce localized tissue destruction through export of a cytotoxic exoprotease. Symptoms include a high fever, nonproductive cough (respiratory secretions are not brought up during coughing), headache, neurological manifestations, and severe bronchopneumonia. Diagnosis depends on isolation of the bacterium, documentation of a rise in antibody titer over time, or a rapid test kit using urine to detect antigens. Treatment begins with supportive measures and the administration of erythromycin or rifampin.

Prevention of Legionnaires’ disease depends on the identification and elimination of the environmental source of L. pneumophila contamination. Chlorination, the heating of water, and the cleaning of water-containing devices can help control the multiplication and spread of Legionella. These control measures are effective because the pathogen does not appear to be spread from person to person.
Since the initial outbreak of this disease in 1976, many outbreaks during summer months have been recognized in all parts of the United States. About 1,000 to 1,400 cases are diagnosed each year, and about 30,000 or more additional mild or subclinical cases are thought to occur. It is estimated that 3 to 6% of all nosocomial pneumonias are due to L. pneumophila, especially among immunocompromised patients.

L. pneumophila also causes an illness called Pontiac fever. This disease, which resembles an allergic disease more than an infection, is characterized by an abrupt onset of fever, headache, dizziness, and muscle pains. It is indistinguishable clinically from the various respiratory syndromes caused by viruses. Pneumonia does not occur. The disease resolves spontaneously within 2 to 5 days. No deaths from Pontiac fever have been reported.

Pontiac fever was first described from an outbreak in a county health department in Pontiac, Michigan. Ninety-five percent of the employees became ill and eventually showed elevated serum titers against L. pneumophila. These bacteria were later isolated from the lungs of guinea pigs exposed to the air of the building. The likely source was water from a defective air conditioner.

Meningitis

Meningitis [Greek meninx, membrane, and -itis, inflammation] is an inflammation of the brain or spinal cord meninges (membranes). Based on the specific cause, it can be divided into bacterial (septic) meningitis and the aseptic meningitis syndrome (table 39.2). As shown by the table, there are many causes of the aseptic meningitis syndrome, only some of which can be treated with antimicrobials. Thus accurate identification of the causative agent is essential to proper treatment of the disease. The immediate sources of the bacteria responsible for meningitis are respiratory secretions from carriers or active cases. The bacteria initially colonize the nasopharynx after which they cross the mucosal barrier and enter the bloodstream and cerebrospinal fluid, where they produce inflammation of the meninges.

The usual symptoms of meningitis include an initial respiratory illness or sore throat interrupted by one of the meningial syndromes: vomiting, headache, lethargy, confusion, and stiffness in the neck and back. Bacterial meningitis can be diagnosed by a Gram stain and culture of the bacteria from cerebrospinal fluid or rapid tests (see table 36.3). Once meningitis is suspected, specific antibiotics (penicillin, chloramphenicol, cefotaxime, ceftriaxone, ofloxacin) are administered immediately. A sharp reduction in the incidence of H. influenzae serotype b infections began in the mid-1980s due to vaccine administration, rifampin prophylaxis of disease contacts, and the availability of more efficacious therapeutic agents. From 1987 through 1999, the incidence of invasive infection among U.S. children less than 5 years of age declined by 95%. Currently, all children at the age of 2 months should be vaccinated with the H. influenzae type b conjugate vaccine.

A person may have meningitis symptoms, but show no microbial agent in Gram-stained specimens, and have negative cultures. In such a case the diagnosis often is aseptic meningitis syndrome. Aseptic meningitis is more difficult to treat, and the prognosis is usually poor.

**Mycobacterium avium-M. intracellulare Pneumonia**

During the past decade it has been discovered that there is an extremely large group of mycobacteria that are normal inhabitants of soil, water, and house dust. Two of these have become noteworthy pathogens in the United States. The two, Mycobacterium avium and Mycobacterium intracellulare, are so closely related that they are referred to as the M. avium complex (MAC).

These mycobacteria are found worldwide and infect a variety of insects, birds, and animals. Both the respiratory and the gastrointestinal tract have been proposed as the portal of entry for the M. avium complex. The gastrointestinal tract is thought to be the most common site of colonization and dissemination in AIDS patients. MAC causes a pulmonary infection in humans similar to M. tuberculosis. Pulmonary MAC is more common in non-AIDS patients, particularly in elderly persons with preexisting pulmonary disease.

Shortly after the recognition of AIDS and the associated opportunistic infections (see table 38.3), it became apparent that one of the more common infections was caused by MAC. Disseminated infection with MAC occurs in 15 to 40% of persons with AIDS in the United States with CD4+ cell counts of less than 100 per cubic millimeter. Disseminated infection with MAC produces disabling symptoms, including fever, malaise, weight loss, night sweats, and diarrhea. Carefully controlled epidemiological studies have shown that MAC shortens survival by 5 to 7 months among persons with AIDS. With more effective antiviral therapy for AIDS and with prolonged survival, the number of cases of disseminated MAC is likely to increase substantially, and its contribution to AIDS mortality will increase.

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**Table 39.2 Causative Agents of Meningitis by Diagnostic Category**

<table>
<thead>
<tr>
<th>Type of Meningitis</th>
<th>Causative Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial (Septic) Meningitis</td>
<td>Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type b, Gram-negative bacilli, Group B streptococci, Listeria monocytogenes, Mycobacterium tuberculosis, Nocardia asteroides, Staphylococcus aureus, Staphylococcus epidermidis</td>
</tr>
<tr>
<td>Aseptic Meningitis Syndrome</td>
<td>Fungi, Amoebae, Syphilis, Mycoplasmas, Leptospires</td>
</tr>
<tr>
<td>Agents Requiring Antimicrobials</td>
<td>Viruses, Cancers, Parasitic cysts, Chemicals</td>
</tr>
</tbody>
</table>

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**Approach to Isolation of Pathogens**

**Table 36.3**

- **Agents Requiring Antimicrobials**: Fungi, Amoebae, Syphilis, Mycoplasmas, Leptospires
- **Agents Requiring Other Treatments**: Viruses, Cancers, Parasitic cysts, Chemicals
MAC can be isolated from sputum, blood, and aspirates of bone marrow. Acid-fast stains are of value in making a diagnosis. The most sensitive method for detection is the commercially available lysis-centrifugation blood culture system (Wampole Laboratories). Although no drugs are currently approved by the FDA for the therapy of MAC, every regimen should contain either azithromycin or clarithromycin or ethambutol as a second drug, and one or more of the following: cefazolin, rifabutin, rifampin, ciprofloxacin, and amikacin.

Pertussis

Pertussis [Latin per, intensive, and tussis, cough], sometimes called “whooping cough,” is caused by the gram-negative bacterium Bordetella pertussis. (B. parapertussis is a closely related species that causes a milder form of the disease.) Pertussis is a highly contagious disease that primarily affects children. It has been estimated that over 95% of the world’s population has experienced either mild or severe symptoms of the disease. Around 500,000 die from the disease each year. However, there are less than around 5,000 cases and less than 10 deaths annually in the United States.

Transmission occurs by inhalation of the bacterium in droplets released from an infected person. The incubation period is 7 to 14 days. Once inside the upper respiratory tract, the bacteria attach to the ciliated epithelial cells by producing adhesins such as the factor called filamentous hemagglutinin, which recognizes a complementary molecule on the cells. After attachment, the bacteria synthesize several toxins (see table 34.6) that are responsible for the symptoms. The most important toxin is pertussis toxin, which causes increased tissue susceptibility to histamine and serotonin, and an increased lymphocyte response. B. pertussis also produces an extracellular invasive adenylate cyclase, and tracheal cytotoxin and demembranotic toxin, which destroy epithelial tissue. In addition, the secretion of a thick mucus impedes ciliary action, and often, ciliated epithelial cells die.

Pertussis is divided into three stages. (1) The catarrhal stage, so named because of the mucous membrane inflammation, which is insidious and resembles the common cold. (2) Prolonged coughing sieges characterize the paroxysmal stage. During this stage the infected person tries to cough up the mucous secretions by making 5 to 15 rapidly consecutive coughs followed by the characteristic whoop—a hurried deep inspiration. The catarrhal and paroxysmal stages last about 6 weeks. (3) Final recovery may take several months (the convalescent stage).

Laboratory diagnosis of pertussis is by culture of the bacterium, fluorescent antibody staining of smears from nasopharyngeal swabs, and serological tests. The development of a strong, lasting immunity takes place after an initial infection. Treatment is with erythromycin, tetracycline, or chloramphenicol. Treatment ameliorates clinical illness when begun during the catarrhal phase and may also reduce the severity of the disease when begun within 2 weeks of the onset of the paroxysmal cough. Prevention is with the DPT vaccine (see p. 765); vaccination of children is recommended when they are 2 to 3 months old (see table 33.1).

Streptococcal Diseases

Streptococci, commonly called strep, are a heterogeneous group of gram-positive bacteria. In this group Streptococcus pyogenes (group A β-hemolytic streptococci; see pp. 530–33) is one of the most important bacterial pathogens. The different serotypes produce (1) extracellular enzymes that break down host molecules; (2) streptokinases, enzymes that activate a host-blood factor that dissolves blood clots; (3) the cytolysins streptolysin O and streptolysin S, which kill host leukocytes; and (4) capsules and M protein that help retard phagocytosis.

S. pyogenes is widely distributed among humans, but usually people are asymptomatic carriers. Individuals with acute infections may spread the pathogen, and transmission can occur through respiratory droplets, direct, or indirect contact. When highly virulent strains appear in schools, they can cause sharp outbreaks of sore throats and scarlet fever. Due to the cumulative buildup of antibodies to many different S. pyogenes serotypes over the years, outbreaks among adults are less frequent.

Diagnosis of a streptococcal infection is based on both clinical and laboratory findings. Several rapid tests are available (see table 36.3). Treatment is with penicillin or erythromycin. Vaccines are not available for streptococcal diseases other than streptococcal pneumonia because of the large number of serotypes.

The best control measure is prevention of bacterial transmission. Individuals with a known infection should be isolated and treated. Personnel working with infected patients should follow standard aseptic procedures.

In the following sections some of the more important human streptococcal diseases are discussed (figure 39.3).

Cellulitis and Erysipelas

Cellulitis is a diffuse, spreading infection of subcutaneous skin tissue. The resulting inflammation is characterized by a defined area of redness (erythema) and the accumulation of fluid (edema).

The most frequently diagnosed skin infection caused by S. pyogenes is impetigo (impetigo also can be caused by S. aureus [figure 39.16]). Impetigo is a superficial cutaneous infection, most commonly seen in children, usually located on the face, and characterized by crusty lesions and vesicles surrounded by a red border. Impetigo is most common in late summer and early fall. The drugs of choice for impetigo are penicillin or erythromycin in those individuals who are allergic to penicillin.

Erysipelas [Greek erythros, red, and pella, skin] is an acute infection and inflammation of the dermal layer of the skin. It occurs primarily in infants and people over 30 years of age with a history of streptococcal sore throat. The skin often develops painful reddish patches that enlarge and thicken with a sharply defined edge (figure 39.4). Recovery usually takes a week or longer if no treatment is given. The drugs of choice for the treatment of erysipelas are erythromycin and penicillin. Erysipelas may recur periodically at the same body site for years.
Invasive Streptococcus A Infections

In the nineteenth century invasive Streptococcus pyogenes infections were a major cause of morbidity and mortality. However, during this century the incidence of severe group A streptococcal infections has declined, especially since the arrival of antibiotic therapy. In the mid-1980s there was a worldwide increase in group A streptococcal sepsis; clusters of rheumatic fever were reported from locations within the United States, and a streptococcal toxic shock–like syndrome emerged. (A virulent strep A infection killed Sesame Street Muppeteer Jim Henson in 1990, and in 1994 the press made headlines with articles on “the flesh-eating invasive disease.”)

The development of invasive strep A disease appears to depend on the presence of specific virulent strains (M-1 and M-3 serotypes) and predisposing host factors (surgical or nonsurgical wounds, diabetes, and other underlying medical problems). A life-threatening infection begins when invasive strep A strains penetrate a mucous membrane or take up residence in a skin lesion such as a bruise. This infection can quickly lead either to necrotizing fasciitis [Greek nekrosis, deadness, Latin fascis, band or bandage, and itis, inflammation] that destroys the sheath covering skeletal muscles or to myositis [Greek myos, muscle, and itis, inflammation], the inflammation and destruction of skeletal muscle and fat tissue. Because necrotizing fasciitis and myositis arise and spread so quickly, they have been colloquially called “galloping gangrene.”

Rapid treatment is necessary to reduce the risk of death, and penicillin G remains the treatment of choice. In addition, surgical removal of dead and dying tissue usually is needed in more advanced cases of necrotizing fasciitis. It is estimated that 10,000 to 15,000 cases of invasive strep A infections occur annually in the United States, and between 5 and 10% of them are associated with necrotizing conditions.

One reason invasive strep A strains are so deadly is that about 85% of them carry the genes for the production of streptococcal pyrogenic exotoxins A and B (Spe exotoxins). Exotoxin A acts as a superantigen. This superantigen quickly stimulates T cells to begin producing abnormally large quantities of cytokines. These cytokines damage the endothelial cells that line blood vessels, causing fluid loss and rapid tissue death from a lack of oxygen. Another pathogenic mechanism involves the secretion of exotoxin B (cysteine protease). Cysteine protease is an enzyme that rapidly destroys tissue by breaking down proteins.

Since 1986 it has been recognized that invasive strep A infections can also trigger a toxic shock–like syndrome (TSLS), characterized by a precipitous drop in blood pressure, failure of multiple organs, and a very high fever. TSLS is caused by an invasive strep A that produces one or more of the streptococcal pyrogenic exotoxins. TSLS has a mortality rate of over 30%.

Because group A streptococci are less contagious than cold or flu viruses, infected individuals do not pose a major threat to people around them. The best preventive measures are simple ones such as covering food, washing hands, and cleansing and medicating wounds.

Poststreptococcal Diseases

The poststreptococcal diseases are glomerulonephritis and rheumatic fever. They occur 1 to 4 weeks after an acute streptococcal infection (hence the term post). Today these two diseases are the
most serious problems associated with streptococcal infections in the United States.

Glomerulonephritis or Bright’s disease is an inflammatory disease of the renal glomeruli, membranous structures within the kidney where blood is filtered. Damage probably results from the deposition of antigen-antibody complexes, possibly involving the streptococcal M protein, in the glomeruli. Thus the disease arises from a type III hypersensitivity reaction (see figure 33.6). The complexes cause destruction of the glomerular membrane, allowing proteins and blood to leak into the urine. Clinically the affected person exhibits edema, fever, hypertension, and hematuria (blood in the urine). The disease occurs primarily among school-age children. Diagnosis is based on the clinical history, physical findings, and confirmatory evidence of prior streptococcal infection. The incidence of glomerulonephritis in the United States is less than 0.5% of streptococcal infections. Penicillin G or erythromycin can be given for any residual streptococci. However, there is no specific therapy once kidney damage has occurred. About 80 to 90% of all cases undergo slow spontaneous healing of the damaged glomeruli, whereas the others develop a chronic form of the disease. The latter may require a kidney transplant or lifelong renal dialysis.

Rheumatic fever is an autoimmune disease characterized by inflammatory lesions involving the heart valves, joints, subcutaneous tissues, and central nervous system. It usually results from a prior streptococcal sore throat infection. The exact mechanism of rheumatic fever development remains unknown. The disease occurs most frequently among children 6 to 15 years of age and manifests itself through a variety of signs and symptoms, making diagnosis difficult. In the United States rheumatic fever has become very rare (less than 0.05% of streptococcal infections), but it occurs 100 times more frequently in tropical countries. Therapy is directed at decreasing the inflammation and fever and controlling cardiac failure. Salicylates and corticosteroids are the mainstays of treatment. Though rheumatic fever is rare, it is still the most common cause of permanent heart valve damage in children.

Scarlet Fever

Scarlet fever (scarlatina) results from a throat infection with a strain of S. pyogenes that carries a lysogenic bacteriophage. This codes for the production of an erythrogenic or rash-inducing toxin that causes shedding of the skin. Scarlet fever is a communicable disease spread by inhalation of infective respiratory droplets. After a 2-day incubation period, a scarlatinal rash appears on the upper chest and then spreads to the remainder of the body. This rash represents the skin’s generalized reaction to the circulating toxin. Along with the rash, the infected individual experiences a sore throat, chills, fever, headache, and a strawberry-colored tongue (figure 39.5). Treatment is with penicillin.

Streptococcal Sore Throat

Streptococcal sore throat is one of the most common bacterial infections of humans and is commonly called strep throat. The β-hemolytic group A streptococci are spread by droplets of saliva or nasal secretions. The incubation period in humans is 2 to 4 days. The incidence of sore throat is greater during the winter and spring months.

The action of the strep bacteria in the throat (pharyngitis) or on the tonsils (tonsillitis) stimulates an inflammatory response and the lysis of leukocytes and erythrocytes. An inflammatory exudate consisting of cells and fluid is released from the blood vessels and deposited in the surrounding tissue. This is accompanied by a general feeling of discomfort or malaise, fever (usually above 101°F), and headache. Prominent physical manifestations include redness, edema, and lymph node enlargement in the throat. Several common rapid test kits are available for diagnosing strep throat. In the absence of complications, the disease is self-limited and disappears within a week. However, treatment with penicillin G benzathine (or erythromycin for penicillin-allergic people) can shorten the infection and clinical syndromes, and is especially important in children for the prevention of complications such as rheumatic fever and glomerulonephritis. Infections in older children and adults tend to be milder and less frequent due in part to the immunity they have developed against the many serotypes encountered in early childhood. Prevention and control measures include proper disposal or cleansing of objects (e.g., facial tissue, handkerchiefs) contaminated by discharges from the infected individual.

Streptococcal Pneumonia

Streptococcal pneumonia is now considered an endogenous infection—that is, it is contracted from one’s own normal microbiota (see figure 31.2). It is caused by the gram-positive Streptococcus pneumoniae, found in the upper respiratory tract (figure 39.6). However, disease usually occurs only in those individuals with predisposing factors such as viral infections of the respiratory tract, physical injury to the tract, alcoholism, or diabetes. About 60 to 80% of all respiratory diseases known as pneumonia are caused by S. pneumoniae. An estimated 150,000 to 300,000

Figure 39.5 Scarlet Fever. The strawberry-colored tongue of this streptococcal disease.
people in the United States contract this form of pneumonia annually, and between 13,000 to 66,000 deaths result.

The primary virulence factor of \textit{S. pneumoniae} is its capsular polysaccharide. The capsular polysaccharide is composed of hyaluronic acid. It is the production of large amounts of hyaluronic capsular polysaccharide that plays an important role in protecting the organism from ingestion and killing by phagocytes (see chapter 34 opener). The pathogenesis is due to the rapid multiplication of the bacteria in alveolar spaces. The bacteria also produce the toxin pneumolysin that destroys host cells. The alveoli fill with blood cells and fluid and become inflamed. The sputum is often rust colored because of blood coughed up from the lungs. The onset of clinical symptoms is usually abrupt, with chills, hard labored breathing, and chest pain. Diagnosis is by chest X ray, biochemical tests, and culture. Penicillin G, cefotaxime, ofloxacin, and ceftriaxone have contributed to a greatly reduced mortality rate. For individuals who are sensitive to penicillin, erythromycin, or tetracycline can be used. Recently a penicillin- and tetracycline-resistant strain of \textit{S. pneumoniae} has appeared in the United States. Pneumococcal vaccines (Pneumovax 23, Pnu-Imune 23) are available for people who are debilitated (e.g., people in chronic-care facilities). The efficacy of the Pneumovax vaccines (pooled collections of 23 different \textit{S. pneumoniae} capsular polysaccharides) is that they generate antibodies to the capsule. When these antibodies are deposited on the surface of the capsule, they become opsonic and enhance phagocytosis. Preventive and control measures include immunization and adequate treatment of infected persons.

\textbf{Tuberculosis}

Over a century ago Robert Koch (see figure 1.4) identified \textit{Mycobacterium tuberculosis} as the causative agent of \textit{tuberculosis} (TB). At the time, TB was rampant, causing 1/7 of all deaths in Europe and 1/3 of deaths among productive young adults. Today TB remains a global health problem of enormous dimension. It is estimated that there are 1 billion (20\%) of the world’s human pop-
In the United States this disease occurs most commonly among the homeless, elderly, malnourished, or alcoholic poor males, minorities, immigrants, prison populations, and Native Americans. More than 26,000 new cases of tuberculosis and over 12,000 deaths are reported annually. Most cases in the United States are caused by the acid-fast *Mycobacterium tuberculosis*, acquired from other humans through droplet nuclei and the respiratory route (figure 39.7). It appears that about 1/4 to 1/3 of active TB cases in the United States may be due to recent transmission. The majority of active cases result from the reactivation of old dormant infections. Worldwide, *M. bovis* and *M. africanum* also cause TB. Transmission to humans from susceptible animal species and their products (e.g., milk) is also possible. Recently there has been a steady yearly increase in the number of TB cases.
as a result of the AIDS epidemic. Available statistics indicate that a close association exists between AIDS and TB. Therefore further spread of HIV infection among the population with a high prevalence of TB infection is resulting in dramatic increases in TB.

Once in the lungs the bacteria are phagocytosed by macrophages and a hypersensitivity response forms small, hard nodules called *tubercles*, which are characteristic of tuberculosis and give the disease its name. The disease process usually stops at this stage, but the bacteria often remain alive within macrophage phagosomes. Resistance to oxidative killing, inhibition of phagosome-lysosome fusion, and inhibition of diffusion of lysosomal enzymes are some of the mechanisms that may explain the survival of *M. tuberculosis* inside macrophages. In time the tubercle may change to a cheeselike consistency and is then called a *caseous lesion*. If such lesions calcify, they are termed Ghon complexes, which show up prominently in a chest X ray. (Often the primary lesion is called the Ghon’s tubercle or Ghon’s focus.) Sometimes the tubercles lesions liquefy and form air-filled *tuberculous cavities*. From these cavities the bacteria can spread to new foci of infections throughout the body. This spreading is often called *miliary tuberculosis* due to the many tubercles the size of millet seeds that are formed in the infected tissue. It also may be called *reactivation tuberculosis* because the bacteria have been reactivated in the initial site of infection.

Persons infected with *M. tuberculosis* develop a cell-mediated immunity due to the bacteria being phagocytosed by macrophages. This immunity involves sensitized T cells (figure 39.7b) and is the basis for the tuberculin skin test (see figure 33.7a). In this test a purified protein derivative (PPD) of *M. tuberculosis* is injected intracutaneously (the Mantoux test). If the person has had tuberculosis, sensitized T cells react with these proteins, and a delayed hypersensitivity reaction occurs within 48 hours. This positive skin reaction appears as an induration (hardening) and reddening of the area around the injection site. Multiple puncture tests such as the Tine test are more convenient but not as accurate.

In a young person a positive skin test possibly indicates active tuberculosis. In older persons it may result from previous disease, vaccination, or a false-positive test. In both cases X rays and bacterial isolation should be completed.

The incubation period is about 4 to 12 weeks, and the disease develops slowly. The symptoms of tuberculosis are fever, fatigue, and weight loss. A cough, which is characteristic of pulmonary involvement, may result in expectoration of bloody sputum.

Laboratory diagnosis of tuberculosis is by isolation of the acid-fast bacterium, chest X ray, commercially available DNA probes, the BACTEC NAP test, and the Mantoux or tuberculin skin test. Both chemotherapy and chemoprophylaxis are carried out by administering isoniazid (INH), plus rifampin, ethambutol, and pyrazinamide. These drugs are administered simultaneously for 12 to 24 months as a way of decreasing the possibility that the patient develops drug resistance.

Recently, new *multi-drug-resistant strains of tuberculosis* (MDR-TB) have developed and are spreading. A multi-drug-resistant strain is defined as *M. tuberculosis* resistant to isoniazid and rifampin, with or without resistance to other drugs. Within the United States drug resistance has increased from 2 to 9% in the past three decades, and similar increases have occurred in many other countries. This has resulted in many cases of marginally treatable, often fatal, disease. Inadequate therapy is the most common means by which resistant bacteria are acquired, and patients who have previously undergone therapy should be presumed to harbor MDR-TB until proved otherwise.

The way in which MDR-TB arises is now known. Tubercle bacilli have spontaneous, predictable rates of chromosomally born mutations that confer resistance to drugs. These mutations are unlinked; hence resistance to one drug is not associated to resistance to an unrelated drug. The emergence of drug resistance represents the survival of random preexisting mutations, not a change caused by exposure to the drug—that the mutations are not linked is the cardinal principle underlying TB chemotherapy. For example, mutations causing resistance to isoniazid or rifampin occur roughly 1 in 10^16 replications of *M. tuberculosis*. The likelihood of spontaneous mutations causing resistance to both isoniazid and rifampin is the sum of these probabilities, or 1 in 10^16. However, these biological mechanisms of resistance break down when chemotherapy is inadequate. In the circumstances of monotherapy, erratic drug ingestion, omission of one or more drugs, suboptimal dosage, poor drug absorption, or an insufficient number of active drugs in a regimen, a susceptible strain on *M. tuberculosis* may become resistant to multiple drugs within a matter of months.

Prevention and control of tuberculosis requires rapid specific therapy to interrupt infectious spread. Retreatment of patients who have multi-drug-resistant tuberculosis should be carried out in programs with comprehensive microbiological, pharmacokinetic, psychosocial, and nutritional support systems. In many countries individuals, especially infants and children, are vaccinated with *bacille Calmette-Guérin* (BCG) vaccine to prevent complications such as meningitis. The BCG vaccine appears to protect about half of those inoculated. Tuberculosis rates also can be lowered by better public health measures and social conditions, for example, a reduction in homelessness and drug abuse.

1. What causes the typical symptoms of diphtheria and how are individuals protected against this disease?
2. What is the environmental source of the bacterium that causes Legionnaires’ disease? Pontiac fever?
3. What are the two major types of meningitis? Why is it so important to determine which type a person has?
4. Name the three stages of pertussis.
5. Name the most important human diseases caused by *Streptococcus pyogenes*. How do they differ from one another?
6. How is tuberculosis diagnosed? Describe the various types of lesions and how they are formed. How do multi-drug-resistant strains of tuberculosis develop?

### 39.2 Arthropod-Borne Diseases

Although arthropod-borne bacterial diseases are generally rare, they are of interest either historically (plague, typhus [see chapter opener quote]) or because they have been newly introduced into
The Hazards of Microbiological Research

The investigation of human pathogens often is a very dangerous matter, and several microbiologists have been killed by the microorganisms they were studying. The study of typhus fever provides a classic example. In 1906 Howard T. Ricketts (1871–1910), an associate professor of pathology at the University of Chicago, became interested in Rocky Mountain spotted fever, a disease that had decimated the Nez Percé and Flathead Indians of Montana. By infecting guinea pigs, he established that a small bacterium was the disease agent and was transmitted by ticks. In late 1909 Ricketts traveled to Mexico to study Mexican typhus.

In 1986 the first case of ehrlichiosis was diagnosed in the United States and shown to be caused by a new bacterial species (table 39.1), *Ehrlichia chaffeensis*. Members of the genus *Ehrlichia* are related to the genus *Rickettsia* and placed in the order *Rickettsiales* of the α-proteobacteria. Since the initial discovery, more than 400 cases have been reported in the United States. *E. chaffeensis* is transmitted from unknown animal vectors to humans by the Lone Star tick (*Amblyomma americanum*). Once inside the human body, *E. chaffeensis* infects circulating monocytes causing a non-specific febrile illness (*human monocytic ehrlichiosis, HME*) that resembles Rocky Mountain spotted fever. Diagnosis involves serological tests and tetracycline is the drug of choice.

In 1994 a new form of ehrlichiosis was discovered. *Human granulocytic ehrlichiosis* (HGE) is transmitted by deer ticks (*Ixodes scapularis*) and possibly dog ticks (*Dermacentor variabilis*), and has been found in 30 states, particularly in the southeastern and south central United States. The causative agent is an *Ehrlichia* species different from *E. chaffeensis*. The disease is characterized by the rapid onset of fever, chills, headaches, and muscle aches. Treatment is with doxycycline.

Epidemic (Louse-Borne) Typhus

Epidemic (louse-borne) typhus is caused by the rickettsia *Rickettsia prowazekii*, which is transmitted from person to person by the body louse (Box 39.1). In the United States a reservoir of *R. prowazekii* also exists in the southern flying squirrel. When a louse feeds on an infected rickettsemic person, the rickettsias infect the insect’s gut and multiply, and large numbers of organisms appear in the feces in about a week. When a louse takes a blood meal, it defecates. The irritation causes the affected individual to scratch the site and contaminate the bite wound with rickettsias.

The rickettsias then spread by way of the bloodstream and infect the endothelial cells of the blood vessels, causing a vasculitis (inflammation of the blood vessels). This produces an abrupt headache, fever, and muscle aches. A rash begins on the upper trunk, and spreads. Without treatment, recovery takes about 2 weeks, though mortality rates are very high (around 50%), especially in the elderly. Recovery from the disease gives a solid immunity and also protects the person from murine typhus.

Diagnosis is by the characteristic rash, symptoms, and the Weil-Felix reaction (Box 39.2). Chloramphenicol and tetracycline are effective against typhus. Control of the human body louse (*Pediculus humanus corporis*) and the conditions that foster its proliferation are mainstays in the prevention of epidemic typhus, although a typhus vaccine is available for high-risk individuals. The importance of louse control and good public hygiene is shown by the prevalence of typhus epidemics during times of war and famine when there is crowding and little attention to the maintenance of proper sanitation. For example, around 30 million cases of typhus fever and 3 million deaths occurred in the Soviet Union and Eastern Europe between 1918 and 1922. The bacteriologist Hans Zinsser believes that Napoleon’s retreat from Russia in 1812 may have been partially provoked by typhus and dysentery epidemics that ravaged the French army. Fewer than 25 cases of epidemic typhus are reported in the United States each year.
The clinical manifestations of murine [Latin mus, muris, mouse or rat] typhus are similar to those of epidemic typhus except that they are milder in degree and the mortality rate is much lower: less than 5%. Diagnosis and treatment also are the same. Rat control and avoidance of rats are preventive measures for the disease. Fewer than 100 cases of endemic typhus are reported in the United States each year.

**Lyme Disease**

Lyme disease (LD, Lyme borreliosis) was first observed and described in 1975 among people of Old Lyme, Connecticut. It has become the most common tick-borne zoonosis in the United States, with more than 10,000 cases being reported annually. In fact, Lyme disease has reached epidemic proportions, and if it were not for AIDS, Lyme disease would be the most important “new” infectious disease (table 39.1) of humans in the United States. The disease is also present in Europe and Asia.

The Lyme spirochetes responsible for this disease comprise at least three species, currently designated *Borrelia burgdorferi* (figure 39.8a), *B. garinii*, and *B. afzelii*. Deer and field mice are the natural hosts. In the northeastern United States, *B. burgdorferi* is transmitted to humans by the bite of the infected deer tick (*Ixodes scapularis*; figure 39.8b). On the Pacific Coast, especially in California, the reservoir is a dusky-footed woodrat, and the tick, *I. pacificus*.

Clinically Lyme disease is a complex illness with three major stages. The initial, localized stage occurs a week to 10 days after an infectious tick bite. The illness usually begins with an expanding, ring-shaped, skin lesion with a red outer border and partial central clearing (figure 39.8c). This often is accompanied by flulike symptoms (malaise and fatigue, headache, fever, and chills). Often the tick bite is unnoticed, and the skin lesion may be missed due to skin coloration or its obscure location such as on the scalp. Thus treatment, which is usually effective at this stage, may not be given because the illness is passed off as “just a touch of the flu.”

The second, disseminated stage may appear weeks or months after the initial infection. It consists of several symptoms such as neurological abnormalities, heart inflammation, and bouts of arthritis (usually in the major joints such as the elbows or knees). Current research indicates that Lyme arthritis might be an autoimmune response to joint cell HLA molecules that are similar to the bacterial antigens. The inflammation that produces organ damage is initiated and possibly perpetuated by the immune response to one or more spirochetal proteins.

Finally, like syphilis, years later the late stage may appear. Infected individuals may develop demyelination of neurons with symptoms resembling Alzheimer’s disease and multiple sclerosis. Behavioral changes also can occur.

Laboratory diagnosis of Lyme’s disease is based on (1) the recovery of the spirochete from the patient, (2) use of the polymerase chain reaction (see section 14.3) for detection of *B. burgdorferi* DNA in urine, or (3) serological testing (Lyme ELISA or Western Blot) for IgM and IgG antibodies to the pathogen. Treatment with amoxicillin or tetracycline early in the illness results in prompt recovery and prevents arthritis and other complications. If nervous system involvement is suspected, ceftriaxone is used since it can cross the blood-brain barrier.

Prevention and control of Lyme disease involves environmental modification (clearing and burning tick habitat) and the application of acaricidal compounds (agents that destroy mites and ticks). An individual’s risk of acquiring Lyme disease may be greatly reduced by education and personal protection. A vaccine, LYMErix, is available for individuals living in areas where Lyme disease is prevalent. The following points should be kept in mind whenever a person is active in an area where Lyme disease or other tick-borne zoonoses occur:

1. It takes a minimum of 24 hours of attachment and feeding for transmission to occur; thus prompt removal of attached ticks will greatly reduce the risk of infection. To remove an embedded tick, one should use tweezers to grasp the tick as close as possible to the skin and then pull with slow, steady pressure in a direction perpendicular to the skin.

2. Because each deer tick life cycle stage is most abundant at a certain time, there are periods when an individual should be most aware of the risk of infection. The most dangerous times are May through July, when the majority of nymphal deer ticks are present and the risk of transmission is greatest.
3. If you must be in the woods, dress accordingly. Wear light-colored pants and good shoes. Tuck the cuffs of your pants into long socks to deny ticks easy entry under your clothes. After coming out of the woods, check all clothes for ticks.

4. Repellents containing high concentrations of DEET (diethyltoluamide) or permanone are available over the counter and are very noxious to ticks. Premethrin kills ticks on contact but is approved only for use on clothing.

5. Immediately after being in a high-risk area, examine your body for bites or itches. Taking a shower and using lots of soap aids in this examination. Areas such as the scalp, armpits, and groin are difficult to examine effectively but are preferred sites for tick attachment. Special attention should be given to these parts of the body.

**Plague**

In the southwestern part of the United States, plague [Latin *plaga*, *pest*] occurs primarily in wild rodents (ground squirrels and prairie dogs). However, massive human epidemics occurred during the Middle Ages, and the disease was known as the Black Death because one of its characteristics is blackish areas on the skin caused by subcutaneous hemorrhages. Infections now occur in humans only sporadically or in limited outbreaks. In the United States approximately 25 cases are reported annually, and the mortality rate is about 15%.

The disease is caused by the gram-negative bacterium *Yersinia pestis*. It is transmitted from rodent to human by the bite of an infected flea, direct contact with infected animals or their products, or inhalation of contaminated airborne droplets (figure 39.9). Once in the human body, the bacteria multiply in the blood and lymph. An important factor in the virulence of *Y. pestis* is its ability to survive and proliferate inside phagocytic cells rather than be killed by them. One of the ways this is accomplished is by the YOPS (yersinal plasmid-encoded outer membrane proteins) that are secreted by the bacterium and act as antiphagocytic proteins to counteract natural defense mechanisms and help the bacteria multiply and disseminate in the host (see figure 34.4).

Symptoms—besides the subcutaneous hemorrhages—include fever and the appearance of enlarged lymph nodes called buboes (hence the old name, *bubonic plague*). In 50 to 70% of the untreated cases, death follows in 3 to 5 days from toxic conditions caused by the large number of bacilli in the blood.

Laboratory diagnosis of plague is by direct microscopic examination, culture of the bacterium, serological tests, the PCR for detection of bacteria in infected fleas, and phage testing. Treatment is with streptomycin, chloramphenicol, or tetracycline, and recovery from the disease gives a good immunity.

**Pneumonic plague** arises (1) from primary exposure to infectious respiratory droplets from a person or cat with respiratory plague or (2) secondary to hematogenous spread in a patient with bubonic or septicemic plague. Pneumonic plague can also arise from accidental inhalation of *Y. pestis* in the laboratory. The mortality rate for this kind of plague is almost 100% if it is not recognized within 12 to 24 hours. Obviously great care must be taken to prevent the spread of airborne infections to personnel taking care of pneumonic plague patients.

Prevention and control involves ectoparasite and rodent control, isolation of human patients, prophylaxis or abortive therapy of exposed persons, and vaccination (USP Plague vaccine) of persons at high risk.
Q Fever

Q fever (Q for query because the cause of the fever was not known for some time) is an acute zoonotic disease caused by the γ-proteobacterium Coxiella burnetii, a strictly intracellular, gram-negative bacterium. C. burnetii is different from Rickettsia in its ability to survive outside host cells by forming a resistant endosporelike body. This bacterium infects both wild animals and livestock. In animals, ticks (many species) transmit C. burnetii, whereas in humans transmission is primarily by inhalation of dust contaminated with bacteria from dried animal feces, urine, or milk. The disease is apt to occur in epidemic form among slaughterhouse workers and sporadically among farmers and veterinarians. Each year, fewer than 100 cases of Q fever are reported in the United States.

In humans, after inhalation of the bacteria, local proliferation occurs in the lungs. This may result in mild respiratory...
symptoms similar to those of atypical pneumonia or influenza. Q fever itself is an acute illness characterized by the sudden onset of severe headache, myalgia (muscle pain), and fever, which may remain very high for more than a month if not treated. Unlike rickettsial diseases, Q fever is not accompanied by a rash. It is rarely fatal, but endocarditis—inflammation of the heart muscle—occurs in about 10% of the cases. Five to ten years may elapse between the initial infection and the appearance of the endocarditis. During this interval the bacteria reside in the liver and often cause hepatitis. Diagnosis is most commonly made serologically. Treatment is with chloramphenicol and tetracycline. Prevention and control consists of vaccinating researchers and others at high occupational risk and in areas of endemic Q fever; cow and sheep milk should be pasteurized before consumption.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is caused by the rickettsia *Rickettsia rickettsii*. Although originally detected in the Rocky Mountain area, most cases of this disease now occur east of the Mississippi River. The disease is transmitted by ticks and usually occurs in people who are or have been in tick-infested areas. There are two principal vectors: *Dermacentor andersoni*, the wood tick, is distributed in the Rocky Mountain states and is active during the spring and early summer. *D. variabilis*, the dog tick, has assumed greater importance and is almost exclusively confined to the eastern half of the United States. Unlike the other rickettsias discussed, *R. rickettsii* can pass from generation to generation of ticks through their eggs in a process known as transovarian passage. No humans or mammals are needed as reservoirs for the continued propagation of this rickettsia in the environment.

When humans contact infected ticks, the rickettsias are either deposited on the skin (if the tick defecates after feeding) and then subsequently rubbed or scratched into the skin, or the rickettsias are deposited into the skin as the tick feeds. Once inside the skin, the rickettsias enter the endothelial cells of small blood vessels, where they multiply and produce a characteristic vasculitis (inflammation of blood vessels).

The disease is characterized by the sudden onset of a headache, high fever, chills, and a skin rash (figure 39.10) that initially appears on the ankles and wrists and then spreads to the trunk of the body. If the disease is not treated, the rickettsias can destroy the blood vessels in the heart, lungs, or kidneys and cause death. Usually, however, severe pathological changes are avoided by antibiotic therapy (chloramphenicol, chlorotetracycline), the development of immune resistance, and supportive therapy. Diagnosis is made through observation of symptoms and signs such as the characteristic rash and by serological tests. The best means of prevention remains the avoidance of tick-infested habitats and animals (see preventive methods for Lyme disease, p. 910). There are approximately 1,000 reported cases of Rocky Mountain spotted fever annually in the United States.

Figure 39.10 Rocky Mountain Spotted Fever. Typical rash occurring on the arms and chest consists of generally distributed, sharply defined macules.

1. What is the causative agent of Lyme disease and how is it transmitted to humans? How does the illness begin? Describe the three stages of Lyme disease.
2. Why is plague sometimes called the Black Death? How is it transmitted? Distinguish between bubonic and pneumonic plague.
3. What two antibiotics are used against most rickettsial infections? What are their symptoms?
5. What is unique about *Coxiella burnetii* compared to the other rickettsias?
6. Describe the symptoms of Rocky Mountain spotted fever.
7. How does transovarian passage occur?

39.3 Direct Contact Diseases

Most of the direct contact bacterial diseases involve the skin or underlying tissues. Others can become disseminated through specific regions of the body. Some of the better-known of these diseases are now discussed.

Anthrax

Anthrax [Greek *anthrax*, coal] is a highly infectious animal disease that can be transmitted to humans by direct contact with infected animals (cattle, goats, sheep) or their products. The causative bacterium is the gram-positive *Bacillus anthracis*. Its endospores can remain viable in soil and animal products for decades (see figure 3.41). Human infection is usually through a cut or abrasion of the skin, resulting in cutaneous anthrax; however, inhaling endospores may result in pulmonary anthrax, also known as woolsorter’s disease. If endospores reach the intestine, gastrointestinal anthrax may result.
Chapter 39 Human Diseases Caused by Bacteria

Treatment for bacterial vaginosis is with metronidazole (Flagyl, MetroGel-Vaginal), a drug that kills the anaerobes that are needed for the continuation of the disease.

Cat-Scratch Disease

Cat-scratch disease (CSD) is a loosely defined syndrome, the cause of which eluded microbiologists for decades. Currently the etiology centers on a recently described gram-negative bacillus, Bartonella henselae (table 39.1).

The diagnosis of CSD is based on the combination of the clinical history of either a cat scratch or bite at the skin surface (primary lesion) and subsequent swelling of the lymph node(s) that drain the inoculation site, and on detection by PCR techniques. This is accompanied by malaise and fever. The typical case of CSD is self-limiting, with abatement of symptoms over a period of days to weeks, and the resolution of the lymphadenopathy over several months.

Chancroid

Chancroid [French chancre, a destructive sore, and Greek eidos, to form], also known as genital ulcer disease, is a sexually transmitted disease caused by the gram-negative bacillus Haemophilus ducreyi (table 39.4). The bacterium enters the skin through a break in the epithelium. After an incubation period of 4 to 7 days, a pustule forms and ruptures, producing a painful circumscribed ulcer with a ragged edge; hence the term genital ulcer disease. Most of the ulcers in males are on the penis and in females at the entrance of the vagina. Genital ulcer disease occurs commonly in the tropics; however, in the past decade there have been major outbreaks in the United States. Worldwide, genital ulcer disease is an important cofactor in the transmission of the AIDS virus; thus it could be an important cofactor in the United States as well. Diagnosis is by isolating H. ducreyi from the ulcers; treatment is with erythromycin or ceftriaxone. Control is by the use of condoms or abstinence.

Chlamydial Pneumonia

Chlamydial pneumonia is caused by Chlamydia pneumoniae (TWAR). Clinically, infections are generally mild; pharyngitis, bronchitis, and sinusitis commonly accompany some lower respiratory tract involvement. Symptoms include fever, a productive cough, sore throat, hoarseness, and pain on swallowing. Infections with C. pneumoniae are common but sporadic; about 50% of adults have antibody to the chlamydiae. Evidence suggests that C. pneumoniae is primarily a human pathogen directly transmitted from human to human by respiratory secretions. Identification of chlamydial pneumonia is based on symptoms and a microimmunofluorescence test. Tetracycline and erythromycin are used for treatment.

In seroepidemiological studies, C. pneumoniae infections have been linked with coronary artery disease as well as vascular disease at other sites. Following a demonstration of C. pneumoniae-like particles in atheromatous tissue by electron microscopy, C. pneumoniae genes and antigens have been detected in atheromas.
Rarely, the microorganism has been recovered in cultures of atheromatous tissue. As a result of these findings, the possible etiologic role of C. pneumoniae in coronary artery disease and systemic atherosclerosis is currently under intense scrutiny.

Gas Gangrene or Clostridial Myonecrosis

Clostridium perfringens, C. novyi, and C. septicum are gram-positive spore-forming rods termed the histotoxic clostridia. They can produce a necrotizing infection of skeletal muscle called gas gangrene [Greek gangraina, an eating sore] or clostridial myonecrosis [myo, muscles, and necrosis, death].

Histotoxic clostridia occur in the soil worldwide and also are part of the normal endogenous microflora of the human large intestine. Contamination of injured tissue with spores from soil containing histotoxic clostridia or bowel flora is the usual means of transmission. Infections are commonly associated with wounds resulting from abortions, automobile accidents, military combat, or frostbite.

If the spores germinate in anaerobic tissue, the bacteria grow and secrete α-toxin, which breaks down muscle tissue. Growth often results in the accumulation of gas (mainly hydrogen as a result of carbohydrate fermentation), and of the toxic breakdown products of skeletal muscle tissue.

Clinical manifestations include severe pain, edema, drainage, and muscle necrosis. The pathology arises from progressive skeletal muscle necrosis due to the effects of α-toxin. Other enzymes produced by the bacteria degrade collagen and tissue, facilitating spread of the disease.

Gas gangrene is a medical emergency. Laboratory diagnosis is through recovery of the appropriate species of clostridia accompanied by the characteristic disease symptoms. Treatment is extensive surgical debridement (removal of all dead tissue), the administration of polyvalent antitoxin, and antimicrobial therapy with penicillin and tetracycline. Hyperbaric oxygen treatment is extensive surgical debridement (removal of all dead tissue), the administration of polyvalent antitoxin, and antimicrobial therapy with penicillin and tetracycline. Hyperbaric oxygen therapy (the use of high concentrations of oxygen at elevated pressures) also is considered effective. The oxygen saturates the infected tissue and thereby prevents the growth of the obligately anaerobic clostridia.

Prevention and control includes debridement of contaminated traumatic wounds plus antimicrobial prophylaxis and prompt treatment of all wound infections. Amputation of limbs often is necessary to prevent further spread of the disease.

Genitourinary Mycoplasmal Diseases

The mycoplasmas Ureaplasma urealyticum and M. hominis are common parasitic microorganisms of the genital tract and their transmission is related to sexual activity (table 39.4). Both mycoplasmas can opportunistically cause inflammation of the reproductive organs of males and females. Because mycoplasmas are not usually cultured by clinicians, management and treatment of these infections depend on a recognition of clinical syndromes and provision for adequate therapy. Tetracyclines are active against most strains; resistant organisms can be treated with erythromycin.

Gonorrhea

Gonorrhea [Greek gono, seed, and rhein, to flow] is an acute, infectious, sexually transmitted disease of the mucous membranes of the genitourinary tract, eye, rectum, and throat (table 39.4). It is caused by the gram-negative, oxidase-positive, diplococcus, Neisseria gonorrhoeae. These bacteria are also referred to as gonococci [pl. of gonococcus; Greek gono, seed, and coccus, berry] and have a worldwide distribution.

Once inside the body the gonococci attach to the microvilli of mucosal cells by means of pili and protein II, which function as adhesins. This attachment prevents the bacteria from being washed away by normal vaginal discharges or by the strong flow of urine. They are then phagocytosed by the mucosal cells and may even be transported through the cells to the intercellular spaces and subepithelial tissue. Phagocytes, such as neutrophils, also may contain gonococci (figure 39.12) inside vesicles. Because the gonococci are intracellular at this time, the host’s defenses have little effect on the bacteria. Following penetration of the bacteria, the host tissue responds locally by the infiltration of mast cells, more PMNs, and plasma cells. These cells are later replaced by fibrous tissue that may lead to urethral closing, or stricture, in males.

In males the incubation period is 2 to 8 days. The onset consists of a urethral discharge of yellow, creamy pus and frequent, painful urination that is accompanied by a burning sensation. In females the disease is more insidious in that few individuals are aware of any symptoms. However, some symptoms may begin 7 to 21 days after infection. These are generally mild; some vaginal discharge may occur. The gonococci also can infect the uterine tubes and surrounding tissues, leading to pelvic inflammatory disease (PID). This occurs in 10 to 20% of infected females. Gonococcal PID is a major cause of sterility and ectopic pregnancies because of scar formation in the uterine tubes. Gonococci disseminate most often during menstruation, a time in which there is an increased concentration of free iron available to the bacteria. In both sexes disseminated gonococcal infection with

![Figure 39.12 Gonorrhea.](image)
bacteremia may occur. This can lead to involvement of the joints (gonorrheal arthritis), heart (gonorrheal endocarditis), or pharynx (gonorrheal pharyngitis). Gonorrheal eye infections occur most often in newborns as they pass through an infected birth canal. The resulting disease is called ophthalmia neonatorum or conjunctivitis of the newborn, which was once a leading cause of blindness in many parts of the world. To prevent this, tetracycline, erythromycin, povodone-iodine, or silver nitrate in dilute solution is placed in the eyes of newborns. This type of treatment is required by law in the United States and many other nations.

Laboratory diagnosis of gonorrhea relies on the successful growth of \( N.\) gonorrhoeae in culture to determine oxidase reaction, Gram stain reaction, and colony and cell morphology. The performance of confirmation tests also is necessary. Because the gonococci are very sensitive to adverse environmental conditions and survive poorly outside the body, special transport media (e.g., PACE) are necessary. A DNA probe (Gen-Probe Pace) for \( N.\) gonorrhoeae has been developed and is used to supplement other diagnostic techniques.

The Centers for Disease Control and Prevention consider four treatment regimens to be coequal after sensitivity testing has been done: (1) penicillin G plus probenecid, (2) ampicillin plus probenecid, (3) ceftriaxone or ofloxacin plus doxycycline for 7 days, or (4) spectinomycin.

Penicillin-resistant strains of gonococci have now developed and occur worldwide. Most of these strains carry a plasmid that directs the formation of penicillinase, a \( \beta \)-lactamase enzyme able to inactivate penicillin G and ampicillin. Since 1980 strains of \( N.\) gonorrhoeae with chromosomally mediated penicillin resistance have developed. Instead of producing a penicillinase, these strains have altered penicillin-binding proteins. Since 1986 tetracycline-resistant \( N.\) gonorrhoeae also have developed.

The most effective method for control of this sexually transmitted disease is public education, diagnosing and treating the asymptomatic patient, condom use, and treating infected individuals quickly to prevent further spread of the disease. Slightly un-}

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**Leprosy**

Leprosy [Greek Lepros, scaly, scabby, rough] or Hansen’s disease is a severely disfiguring skin disease caused by Mycobacterium leprae (see figure 24.9). The only reservoirs of proved significance are humans. The disease most often occurs in tropical countries, where there are more than 14 million cases. An estimated 4,000 cases exist in the United States, with approximately 200 to 300 new cases reported annually.

Transmission of leprosy is most likely to occur when individuals are exposed for prolonged periods to infected individuals who shed large numbers of \( M.\) leprae. Nasal secretions probably are the infectious material for family contacts.

The incubation period is about 3 to 5 years but may be much longer, and the disease progresses slowly. The bacterium invades peripheral nerve and skin cells and becomes an obligately intra-cellular parasite. It is most frequently found in the Schwann cells that surround peripheral nerve axons and in mononuclear phagocytes. The earliest symptom of leprosy is usually a slightly pigmented skin eruption several centimeters in diameter. Approximately 75% of all individuals with this early solitary lesion heal spontaneously because of the cell-mediated immune response to \( M.\) leprae. However, in some individuals this immune response may be so weak that one of two distinct forms of the disease occurs: tuberculoid or lepromatous leprosy (figure 39.13).

**Tuberculoid (neural) leprosy** is a mild, nonprogressive form of leprosy associated with a delayed-type hypersensitivity reaction (see section 33.2) to antigens on the surface of \( M.\) leprae. It is characterized by damaged nerves and regions of the skin that have lost sensation and are surrounded by a border of nodules (figure 39.14). Afflicted individuals who do not develop hypersensitivity have a relentlessly progressive form of the disease, called lepromatous (progressive) leprosy, in which large numbers of \( M.\) leprae develop in the skin cells. The bacteria kill skin tissue, leading to a progressive loss of facial features, fingers, toes, and other structures. Moreover, disfiguring nodules form all over the body. Nerves are also infected, but usually are less damaged than in tuberculoid leprosy.

Because the leprosy bacillus cannot be cultured in vitro, laboratory diagnosis is supported by the demonstration of the bacterium in biopsy specimens and by acid-fast staining. Serodiagnostic methods, such as the fluorescent leprosy antibody absorption test, DNA amplification, and ELISA have recently been developed.
Treatment is long-term with the sulfone drug diacetyl dapsone and rifampin, with or without clofazimine. Alternative drugs are ethionamide or protionamide. Use of *Mycobacterium vaccae* in conjunction with the drugs shortens the duration of drug therapy and speeds recovery from the disease.

There is good evidence that the nine-banded armadillo is an animal reservoir for the leprosy bacillus in the United States but plays no role in transmission of leprosy to humans. Identification and treatment of patients with leprosy is the key to control. Children of presumably contagious parents should be given chemoprophylactic drugs until treatment of the parents has made them noninfectious.

2. Define the following terms: cutaneous anthrax, bacterial vaginosis, pelvic inflammatory disease, ophthalmia neonatorum, tuberculoid and lepromatous leprosy.
3. How does an infant acquire inclusion conjunctivitis?
4. How do humans contract chlamydial pneumonia?

**Lymphogranuloma Venereum**

*Lymphogranuloma venereum* (LGV) is a sexually transmitted disease (table 39.4) caused by *Chlamydia trachomatis* serotypes L1–L3. It has a worldwide distribution but is more common in tropical climates.

LGV proceeds through three phases. (1) In the primary phase a small ulcer appears several days to several weeks after a person is exposed to the chlamydiae. The ulcer may appear on the penis in males or on the labia or vagina in females. The ulcer heals quickly and leaves no scar. (2) The secondary phase begins 2 to 6 weeks after exposure, when the chlamydiae infect lymphoid cells, causing the regional lymph nodes to become enlarged and tender; such nodes are called buboes (figure 39.15). Systemic symptoms such as fever, chills, and anorexia are common. (3) If the disease is not treated, a late phase ensues. This results from fibrotic changes and abnormal lymphatic drainage that produces fistulas (abnormal passages leading from an abscess or a hollow organ to the body surface or from one hollow organ to another) and urethral or rectal strictures (a decrease in size). An untreatable fluid accumulation in the penis, scrotum, or vaginal area may result.

The disease is detected by staining infected cells with iodine to observe inclusions (chlamydia-filled vacuoles), culture of the chlamydiae from a bubo, nucleic acid probes, or by the detection of a high antibody titer to LGV. Treatment in the early phases consists of aspiration of the buboes and administration of drugs: tetracycline, doxycycline, erythromycin, or cefotaxime. The late phase may require surgery. The methods used for the control of LGV are the same as for other sexually transmitted diseases: reduction in promiscuity, use of condoms, and early diagnosis and treatment of infected individuals. About 300 cases of LGV occur annually in the United States.

**Mycoplasmal Pneumonia**

Typical pneumonia has a bacterial origin. If a bacterial pathogen cannot be isolated, the pneumonia is termed atypical and a virus is usually suspected. If viruses can’t be detected, then *mycoplasmal*
Nongonococcal Urethritis

Nongonococcal urethritis (NGU) is any inflammation of the urethra not due to the bacterium Neisseria gonorrhoeae. This condition is caused both by nonmicrobial factors such as catheters and drugs and by infectious microorganisms. The most important causative agents are C. trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Trichomonas vaginalis, Candida albicans, and herpes simplex viruses. Most infections are acquired sexually (table 39.4), and of these, approximately 50% are Chlamydia infections. NGU caused by chlamydia is probably the most common sexually transmitted disease in the United States, with over 10 million Americans infected. It is endemic throughout the world.

Symptoms of NGU vary widely. Males may have few or no manifestations of disease; however, complications can exist. These include a urethral discharge, itching, and inflammation of the male reproductive structures. Females may be asymptomatic or have a severe infection called pelvic inflammatory disease (PID) that often leads to sterility. Chlamydia may account for as many as 200,000 to 400,000 cases of PID annually in the United States. In the pregnant female, a chlamydial infection is especially serious because it is directly related to miscarriage, stillbirth, inclusion conjunctivitis, and infant pneumonia.

Diagnosis of NGU requires the demonstration of a leukocyte exudate and exclusion of urethral gonorrhea by Gram stain and culture. Several rapid tests for detecting Chlamydia in urine specimens are also available. Treatment is with tetracycline, doxycycline, erythromycin, or sulfafoxazole.

Peptic Ulcer Disease and Gastritis

A gram-negative, microaerophilic spiral bacillus found in gastric biopsy specimens from patients with histologic gastritis [Greek gastér, stomach, and itis, inflammation] was successfully cultured in Perth, Australia, in 1982 and named Campylobacter pylori. In 1993 its name was changed to Helicobacter pylori. It now appears that this bacterium is responsible for most cases of chronic gastritis not associated with another known primary cause (e.g., autoimmune gastritis or eosinophilic gastritis), and it is the leading factor in the pathogenesis of peptic ulcer disease. In addition, there are strong positive correlations between gastric cancer rates and H. pylori infection rates in certain populations.

The evidence for H. pylori as a gastrointestinal pathogen is now very strong, if not overwhelming. For example, H. pylori has been isolated from the gastric mucosa (figure 39.16) of 95% of patients with gastric ulcer disease and virtually 100% of those patients with chronic gastritis, but not from healthy tissue.

H. pylori colonizes only gastric mucus-secreting cells, beneath the gastric mucous layers, and surface fimbriae are believed to be one of the adhesins associated with this process. H. pylori binds to Lewis antigens (which are part of the blood group antigens that determine blood group O) and to the monosaccharide sialic acid, also found in the glycoproteins on the surface of gastric epithelial cells. After attachment, the bacterium moves into the mucous layer.

H. pylori is also a strong producer of urease. Urease activity may create an alkaline environment by urea hydrolysis to produce ammonia that protects the bacterium from gastric acid until it colonizes under the layer of mucus in the stomach. The potential virulence factors responsible for epithelial cell damage and inflammation probably include proteases, phospholipases, cytokines, and cytotoxins.
of custodial institutions and nursing homes. Transmission comes from evidence of clustering within families that it is spread by food or water. Support for the person-to-personogenous source cannot be completely ruled out, and some think from person to person, although infection from a common ex-

**Figure 39.16 Peptic Ulcer Disease.** Scanning electron micrograph (× 3,441) of *Helicobacter pylori* adhering to gastric cells.

Approximately 50% of the world’s population is estimated to be infected with *H. pylori*. *H. pylori* is most likely transmitted from person to person, although infection from a common exogenous source cannot be completely ruled out, and some think that it is spread by food or water. Support for the person-to-person transmission comes from evidence of clustering within families and from reports of higher than expected prevalences in residents of custodial institutions and nursing homes.

Laboratory identification of *H. pylori* is by culture of gastric biopsy specimens, examination of stained biopsies for the presence of bacteria, detection of serum IgG (*Pyloriset EIA-G, Malakit Helicobacter pylori*), the urea breath test, urinary excretion of [15N] ammonia, or detection of urease activity in the biopsies. Treatment is with bismuth subsalicylate (Pepto-

Psittacosis (Ornithosis)

**Psittacosis (ornithosis)** is a worldwide infectious disease of birds that is transmissible to humans. It was first described in association with parrots and parakeets, both of which are psittacine birds. The disease is now recognized in many other birds—among them, pigeons, chickens, ducks, and turkeys—and the general term ornithosis [Latin *ornis*, bird] is used.

Ornithosis is caused by *Chlamydia psittaci*. Humans contract this disease either by handling infected birds or by inhaling dried bird excreta that contains viable *C. psittaci*. Ornithosis is recog-

ized as an occupational hazard within the poultry industry, particularly to workers in turkey processing plants.

After entering the respiratory tract, the chlamydiae are transported to the cells of the liver and spleen. They multiply within these cells and then invade the lungs, where they cause inflammation, hemorrhaging, and pneumonia.

Laboratory diagnosis is either by isolation of *C. psittaci* from blood or sputum, or by serological studies. Treatment is with tetracycline. Because of antibiotic therapy, the mortality rate has dropped from 20 to 2%. Between 100 and 200 cases of ornithosis are reported annually in the United States. Prevention and control is by chemoprophylaxis (tetracycline) for pet birds and poultry, although this can lead to the development of antibiotic resistance and should be discouraged.

**Staphylococcal Diseases**

The genus *Staphylococcus* consists of gram-positive cocci, 0.5 to 1.5 μm in diameter, occurring singly, in pairs, and in tetrads, and characteristically dividing in more than one plane to form irregular clusters. The cell wall contains peptidoglycan and teichoic acid. Staphylococci are facultative anaerobes and usually catalase positive.

Staphylococci are among the most important bacteria that cause disease in humans. They are normal inhabitants of the upper respiratory tract, skin, intestine, and vagina (see figure 31.2). Staphylococci, with pneumococci and streptococci, are members of a group of invasive gram-positive bacteria known as the pyogenic (or pus-producing) cocci. These bacteria cause various suppurrative, or pus-forming diseases (e.g., boils, carbuncles, folliculitis, impetigo contagiosa, scalded-skin syndrome) in humans.

Staphylococci can be divided into pathogenic and relatively nonpathogenic strains based on the synthesis of the enzyme coagulase. Coagulase-positive strains, such as *S. aureus* (see figure 23.12a), often produce a yellow carotenoid pigment—which has led to their being commonly called golden staph (see figure 5.9)—and cause severe chronic infections. Coagulase-negative staphylococci (*CoNS*) such as *S. epidermidis* do not produce coagulase, are nonpigmented, and are generally less invasive but have increasingly been associated (as opportunistic pathogens) with serious nosocomial infections.

Staphylococci are further classified into slime producers (SP) and non-slime producers (NSP). The ability to produce slime has been proposed as a marker for pathogenic strains of staphylococci (figure 39.17a).

**Slime** is a viscous extracellular glycoconjugate that allows these bacteria to adhere to smooth surfaces such as prosthetic medical devices and catheters. Scanning electron microscopy has clearly demonstrated that biofilms (figure 39.17b) consisting of staphylococci encased in a slimy matrix are formed in association with biomaterial-associated infections (Box 39.3). Slime also appears to inhibit neutrophil chemotaxis, phagocytosis, and the antimicrobial agents vancomycin and teicoplanin.

Staphylococci, harbored by either an asymptomatic carrier or a person with the disease, can be spread by the hands, expelled from the respiratory tract, or transported in or on animate and inanimate objects. Staphylococci can produce disease in almost
every organ and tissue of the body (figure 39.18). However, it should be emphasized that staphylococcal disease, for the most part, occurs in people whose defensive mechanisms have been compromised, such as those in hospitals.

Staphylococci produce disease through their ability to multiply and spread widely in tissues and through their production of many extracellular substances (table 39.3). Some of these substances are exotoxins, and others are enzymes thought to be involved in staphylococcal invasiveness. Many toxin genes are carried on plasmids; in some cases genes responsible for pathogenicity reside on both a plasmid and the host chromosome.

**Box 39.3**

**Biofilms**

Biofilms consist of microorganisms immobilized at a substratum surface and typically embedded in an organic polymer matrix of microbial origin (see section 28.4). They develop on virtually all surfaces immersed in natural aqueous environments, including both biological (aquatic plants and animals) and abiological (concrete, metal, plastics, stones). Biofilms form particularly rapidly in flowing aqueous systems where a regular nutrient supply is provided to the microorganisms. Extensive microbial growth, accompanied by excretion of copious amounts of extracellular organic polymers, thus leads to the formation of visible slimy layers (biofilms) on solid surfaces.

Most of the human gastrointestinal tract is colonized by specific groups of microorganisms (the normal indigenous microbiota; see section 31.2) that give rise to natural biofilms. At times, these natural biofilms provide protection for pathogenic species, allowing them to colonize the host.

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Insertion of a prosthetic device into the human body often leads to the formation of biofilms on the surface of the device. The microorganisms primarily involved are *Staphylococcus epidermidis* (figure 39.17b), other coagulase-negative staphylococci, and gram-negative bacteria. These normal skin inhabitants possess the ability to tenaciously adhere to the surfaces of inanimate prosthetic devices. Within the biofilms they are protected from the body’s normal defense mechanisms and also from antibiotics; thus the biofilm also provides a source of infection for other parts of the body as bacteria detach during biofilm sloughing.

Some examples of biofilms of medical importance include:

1. The deaths following massive infections of patients receiving the Jarvik 7 artificial hearts
2. Cystic fibrosis patients harboring great numbers of *Pseudomonas aeruginosa* that produce large amounts of alginate polymers, which inhibit the diffusion of antibiotics
3. Teeth, where biofilm forms plaque that leads to tooth decay (figure 39.25)
4. Contact lenses, where bacteria may produce severe eye irritation, inflammation, and infection
5. Air-conditioning and other water retention systems where potentially pathogenic bacteria, such as *Legionella* species, may be protected from the effects of chlorination by biofilms

**Figure 39.17** Slime and Biofilms. *S. aureus* and certain coagulase-negative staphylococci produce a viscous extracellular glycoconjugate called slime. (a) Cells of *S. aureus*, one of which produces a slime layer (arrowhead; transmission electron microscopy, ×10,000). (b) A biofilm on a venous catheter consisting of *S. epidermidis* and slime. The slime encases and adheres the bacterial colonies to the catheter (scanning electron micrograph, ×6,000).
The pathogenic capacity of a particular *S. aureus* strain is due to the combined effect of extracellular factors and toxins, together with the invasive properties of the strain. At one end of the disease spectrum is staphylococcal food poisoning, caused solely by the ingestion of preformed enterotoxin (Table 39.3). At the other end of the spectrum are staphylococcal bacteremia and disseminated abscesses in most organs of the body.

**Table 39.3** Various Enzymes and Toxins Produced by *Staphylococci*

<table>
<thead>
<tr>
<th>Product</th>
<th>Physiological Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactamase</td>
<td>Breaks down penicillin</td>
</tr>
<tr>
<td>Catalase</td>
<td>Converts hydrogen peroxide into water and oxygen and reduces killing by phagocytosis</td>
</tr>
<tr>
<td>Coagulase</td>
<td>Reacts with prothrombin to form a complex that can cleave fibrinogen and cause the formation of a fibrin clot; fibrin may also be deposited on the surface of staphylococci, which may protect them from destruction by phagocytic cells; coagulase production is synonymous with invasive pathogenic potential</td>
</tr>
<tr>
<td>DNase</td>
<td>Destroys DNA</td>
</tr>
<tr>
<td>Enterotoxins</td>
<td>Are divided into heat-stable toxins of six known types (A, B, C1, C2, D, E); responsible for the gastrointestinal upset typical of food poisoning</td>
</tr>
<tr>
<td>Exfoliative toxins</td>
<td>Causes loss of the surface layers of the skin in scalded-skin syndrome (A and B (superantigens))</td>
</tr>
<tr>
<td>Hemolysins</td>
<td>Alpha hemolysin destroys erythrocytes and causes skin destruction</td>
</tr>
<tr>
<td></td>
<td>Beta hemolysin destroys erythrocytes and sphingomyelin around nerves</td>
</tr>
<tr>
<td></td>
<td>Gamma hemolysin destroys erythrocytes</td>
</tr>
<tr>
<td></td>
<td>Delta hemolysin destroys erythrocytes</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>Also known as spreading factor; breaks down hyaluronic acid located between cells, allowing for penetration and spread of bacteria</td>
</tr>
<tr>
<td>Panton-Valentine leucocidin</td>
<td>Inhibits phagocytosis by granulocytes and can destroy these cells by forming pores in their phagosomal membranes</td>
</tr>
<tr>
<td>Lipases</td>
<td>Break down lipids</td>
</tr>
<tr>
<td>Nuclease</td>
<td>Breaks down nucleic acids</td>
</tr>
<tr>
<td>Protein A</td>
<td>Is antiphagocytic by competing with neutrophils for the Fc portion of specific opsonins</td>
</tr>
<tr>
<td>Proteases</td>
<td>Break down proteins</td>
</tr>
<tr>
<td>Toxic shock syndrome toxin-1</td>
<td>Is associated with the fever, shock, and multisystem involvement of toxic shock syndrome (a superantigen)</td>
</tr>
</tbody>
</table>

The classic example of the staphylococcal lesion is the localized abscess (Figure 39.19a–d). When *S. aureus* becomes established in a hair follicle, tissue necrosis results. Coagulase is produced and forms a fibrin wall around the lesion that limits the spread. Within the center of the lesion, liquefaction of necrotic tissue occurs, and the abscess spreads in the direction of least resistance. The abscess may be either a furuncle (boil) or a carbuncle. The central necrotic tissue drains, and healing eventually occurs. However, the bacteria may spread from any focus by the lymphatics and bloodstream to other parts of the body.

**Figure 39.18** Staphylococcal Diseases. The sites of the major staphylococcal infections of humans are indicated by the above numbers.

1 Tissue where *S. aureus* is often found but does not normally cause disease
2 Pimples and impetigo
3 Boils and carbuncles on any surface area
4 Wound infections and abscesses
5 Spread to lymph nodes and to blood (sepsisemia), resulting in widespread seeding
6 Osteomyelitis
7 Endocarditis
8 Meningitis
9 Enteritis and enterotoxin poisoning (food poisoning)
10 Nephritis
11 Respiratory infections: Pharyngitis, Laryngitis, Bronchitis, Pneumonia

Diseases that may be caused by *S. aureus* are:

1  Tissue where *S. aureus* is often found but does not normally cause disease
2  Pimples and impetigo
3  Boils and carbuncles on any surface area
4  Wound infections and abscesses
5  Spread to lymph nodes and to blood (sepsisemia), resulting in widespread seeding

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Newborn infants and children can develop a superficial skin infection characterized by the presence of encrusted pustules (figure 39.19e). This disease, called impetigo contagiosa, is caused by *S. aureus* and group A streptococci. It is contagious and can spread rapidly through a nursery or school. It usually occurs in areas where sanitation and personal hygiene are poor.

**Toxic shock syndrome (TSS)** is a staphylococcal disease with potentially serious consequences. Most cases of this syndrome have occurred in females who use superabsorbent tampons during menstruation. However, the toxin associated with this syndrome is also produced in men and in nonmenstruating women by *S. aureus* present at sites other than the genital area (e.g., in surgical wound infections). Toxic shock syndrome is characterized by low blood pressure, fever, diarrhea, an extensive skin rash, and shedding of the skin. These symptoms are caused by the toxic shock syndrome toxin-1 (TSST-1 is a superantigen; see section 32.2) released by the *S. aureus* (table 39.3), but several other enterotoxins (SEB and SEC₁) also may be involved.

Several hundred cases of toxic shock syndrome are reported annually in the United States.

**Staphylococcal scalded skin syndrome (SSSS)** is a third example of a common staphylococcal disease (figure 39.19f). SSSS is caused by strains of *S. aureus* that carry a plasmid-borne gene for the exfoliative toxin or exfoliatin (sometimes the toxin gene is on the bacterial chromosome instead). Like TSST-1, exfoliatin is a superantigen. In this disease the epidermis peels off to reveal a red area underneath—thus the name of the disease. SSSS is seen most commonly in infants and children, and neonatal nurseries occasionally suffer large outbreaks of the disease.

The definitive diagnosis of staphylococcal disease can be made only by isolation and identification of the staphylococcus involved. This requires culture, catalase, and coagulase tests; serology; DNA fingerprinting; and phage typing. Commercial rapid test kits also are available. There is no specific prevention for staphylococcal disease. The mainstay of treatment is the administration of specific antibiotics: penicillin, cloxacillin, methicillin, vancomycin, oxacillin, ce-

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**Figure 39.19 Staphylococcal Skin Infections.** (a) Superficial folliculitis in which raised, domed pustules form around hair follicles. (b) In deep folliculitis the microorganism invades the deep portion of the follicle and dermis. (c) A furuncle arises when a large abscess forms around a hair follicle. (d) A carbuncle consists of a multilocular abscess around several hair follicles. (e) Impetigo on the neck of 2-year-old male. (f) Scalded skin syndrome in a 1-week-old premature male infant. Reddened areas of skin peel off, leaving “scalded”-looking moist areas.
During the late 1950s and early 1960s, *Staphylococcus aureus* caused considerable morbidity and mortality as a nosocomial, or hospital-acquired, pathogen. Since then, penicillinase-resistant, semisynthetic penicillins have proved to be successful antimicrobial agents in the treatment of staphylococcal infections. Unfortunately, methicillin-resistant *S. aureus* (MRSA) strains have recently emerged as a major nosocomial problem. One way in which staphylococci become resistant is through acquisition of a chromosomal gene (*mecA*) that encodes an alternate target protein which is not inactivated by methicillin. The majority of the strains are resistant to several of the most commonly used antimicrobial agents, including macrolides, aminoglycosides, and the beta-lactam antibiotics, including the latest generation of cephalosporins. Serious infections by methicillin-resistant strains have been most often successfully treated with an older, potentially toxic antibiotic, vancomycin. However, strains of *Enterococcus* and *Staphylococcus* recently have become resistant to vancomycin.

Recently, methicillin-resistant *S. epidermidis* strains also have emerged as a nosocomial problem, especially in individuals with prosthetic heart valves or in people who have undergone other forms of cardiac surgery. Resistance to methicillin also may extend to the cephalosporin antibiotics. Difficulties in performing in vitro tests that adequately recognize cephalosporin resistance of these strains continue to exist. Serious infections due to methicillin-resistant *S. epidermidis* have been successfully treated with combination therapy, including vancomycin plus rifampin or an aminoglycoside.

**Box 39.4**

**Resistant Staphylococci**

During the late 1950s and early 1960s, *Staphylococcus aureus* caused considerable morbidity and mortality as a nosocomial, or hospital-acquired, pathogen. Since then, penicillinase-resistant, semisynthetic penicillins have proved to be successful antimicrobial agents in the treatment of staphylococcal infections. Unfortunately, methicillin-resistant *S. aureus* (MRSA) strains have recently emerged as a major nosocomial problem. One way in which staphylococci become resistant is through acquisition of a chromosomal gene (*mecA*) that encodes an alternate target protein which is not inactivated by methicillin. The majority of the strains are resistant to several of the most commonly used antimicrobial agents, including macrolides, aminoglycosides, and the beta-lactam antibiotics, including the latest generation of cephalosporins. Serious infections by methicillin-resistant strains have been most often successfully treated with an older, potentially toxic antibiotic, vancomycin. However, strains of *Enterococcus* and *Staphylococcus* recently have become resistant to vancomycin.

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**Figure 39.20** Syphilis. (a) Primary syphilitic chancre of the penis. (b) Palmar lesions of secondary syphilis. (c) Ruptured gumma and ulcer of upper hard palate of the mouth.

Syphilis

Venereal syphilis [Greek syn, together, and philein, to love] is a contagious sexually transmitted disease (table 39.4) caused by the spirochete *Treponema pallidum* subsp. *pallidum* (*T. pallidum*, see figure 21.15b). Congenital syphilis is the disease acquired in utero from the mother.

*T. pallidum* enters the body through mucous membranes or minor breaks or abrasions of the skin. It migrates to the regional lymph nodes and rapidly spreads throughout the body. The disease is not highly contagious, and there is only about a 1 in 10 chance of acquiring it from a single exposure to an infected sex partner.

Three recognizable stages of syphilis occur in untreated adults. In the primary stage, after an incubation period of about 10 days to 3 weeks or more, the initial symptom is a small, painless, reddened ulcer, or chancre [French canker; a destructive sore] with a hard ridge that appears at the infection site (figure 39.20a) and contains spirochetes. Contact with the chancre during sexual intercourse may result in disease transmission. In about 1/3 of the cases, the disease does not progress further and the chancre disappears.
Chapter 39 Human Diseases Caused by Bacteria

Serological tests are positive in about 80% of the individuals during this stage (figure 39.21). In the remaining cases the spirochetes enter the bloodstream and are distributed throughout the body.

Within 2 to 10 weeks after the primary lesion, the disease may enter the secondary stage, which is characterized by a skin rash (figure 39.20b). By this time 100% of the individuals are serologically positive. Other symptoms during this stage include the loss of patches of hair, malaise, and fever. Both the chancre and the rash lesions are infectious.

After several weeks the disease becomes latent. During the latent period the disease is not normally infectious, except for possible transmission from mother to fetus (congenital syphilis). After many years a tertiary stage develops in about 40% of untreated individuals with secondary syphilis. During this stage degenerative lesions called* gummas* (figure 39.20c) form in the skin, bone, and nervous system as the result of hypersensitivity reactions. This stage also is characterized by a great reduction in the number of spirochetes in the body. Involvement of the central nervous system may result in tissue loss that can lead to mental retardation, blindness, a “shuffle” walk (tabes), or insanity. Many of these symptoms have been associated with such well-known people as Al Capone, Francisco Goya, Henry VIII, Adolf Hitler, Scott Joplin, Friedrich Nietzsche, Franz Schubert, Oscar Wilde, and Kaiser Wilhelm (Box 39.5).

Diagnosis of syphilis is through a clinical history, a thorough physical examination, and dark-field and immunofluorescence examination of fluids from the lesions (except oral lesions) for typical motile or fluorescent spirochetes. Because humans respond to *T. pallidum* with the formation of antitreponemal antibody and a complement-fixing reagent, serological tests are very informative. Examples include tests for nontreponemal antigens (VDRL, Venereal Disease Research Laboratories test; RPR, Rapid Plasma Reagin test; complement fixation or the Wassermann test) and treponemal antibodies (FTA-ABS, fluorescent treponemal antibody-absorption test; TPI, *T. pallidum* immobilization; T. pallidum complement fixation; TPHA, *T. pallidum* hemagglutination).

Treatment in the early stages of the disease is easily accomplished with long-acting benzathine penicillin G or aqueous procaine penicillin. Later stages of syphilis are more difficult to treat with drugs and require much larger doses over a longer period. For example, in neurosyphilis cases, treponemes occasionally survive such drug treatment. Immunity to syphilis is not complete, and subsequent infections can occur once the first infection has spontaneously disappeared or has been eliminated with antibiotics.

Prevention and control of syphilis depends on (1) public education (2) prompt and adequate treatment of all new cases, (3) follow-up on sources of infection and contact so they can be treated, (4) sexual hygiene, and (5) prophylaxis (condoms) to prevent exposure. At present, the incidence of syphilis, as well as other sexually transmitted diseases, is rising in most parts of the world. In the United States around 50,000 cases of primary and secondary syphilis in the civilian population and about 1,000 cases of congenital syphilis are reported annually. The highest incidence is among those 20 to 39 years of age.

**Tetanus**

Tetanus [Greek tetanos, to stretch] is caused by *Clostridium tetani*, an anaerobic gram-positive spore former (see figure 23.6b). The endospores of *C. tetani* are commonly found in hospital environments, in soil and dust, and in the feces of many farm animals and humans.

Transmission to humans is associated with skin wounds. Any break in the skin can allow *C. tetani* endospores to enter, and if the oxygen tension is low enough, the endospores germinate. When the bacteria die and lyse, the neurotoxin tetanospsamin is released. Tetanospsamin is an endopeptidase that selectively cleaves the synaptic vesicle membrane protein synaptobrevin. This prevents exocytosis and release of inhibitory neurotransmitters (gamma-aminobutyric acid and glycine) at synapses within the spinal cord motor nerves. The result is uncontrolled stimulation of skeletal muscles.

Early in the course of the disease, tetanospsamin causes tension or cramping and twisting in skeletal muscles surrounding the wound and tightness of the jaw muscles. With more advanced dis-
Syphilis was first recognized in Europe near the end of the fifteenth century. During this time the disease reached epidemic proportions in the Mediterranean areas. According to one hypothesis, syphilis is of New World origin and Christopher Columbus (1451–1506) and his crew acquired it in the West Indies and introduced it into Spain after returning from their historic voyage. Another hypothesis is that syphilis had been endemic for centuries in Africa and may have been transported to Europe at the same time that vast migrations of the civilian population were occurring (1500).

Syphilis was initially variously called the Italian disease, the French disease, and the great pox as distinguished from smallpox. In 1530 the Italian physician and poet Girolamo Fracastoro wrote Syphilis sive Morbus Gallicus (Syphilis or the French Disease). In this poem a Spanish shepherd named Syphilis is punished for being disrespectful to the gods by being cursed with the disease. Several years later Fracastoro published a series of papers in which he described the possible mode of transmission of the “seeds” of syphilis through sexual contact.

Its venereal transmission was not definitely shown until the eighteenth century. The term venereal is derived from the name Venus, the Roman goddess of love. Recognition of the different stages of syphilis was demonstrated in 1838 by Philippe Ricord, who reported his observations on more than 2,500 human inoculations. In 1905 Fritz Schaudinn and Erich Hoffmann discovered the causative bacterium, and in 1906 August von Wassermann introduced the diagnostic test that bears his name. In 1909 Paul Ehrlich introduced an arsenic derivative, arsphenamine or salvarsan, as therapy. During this period, an anonymous limerick aptly described the course of this disease:

There was a young man from Black Bay
Who thought syphilis just went away

He believed that a chancre
Was only a canker
That healed in a week and a day.

But now he has “acne vulgaris”—
(Or whatever they call it in Paris);
On his skin it has spread
From his feet to his head,
And his friends want to know where his hair is.

There’s more to his terrible plight:
His pupils won’t close in the light
His heart is cavorting,
His wife is aborting,
And he squints through his gun-barrel sight.

Arthralgia cuts into his slumber;
His aorta is in need of a plumber;
But now he has tabes,
And sabre-shinned babies,
While of gummas he has quite a number.

He’s been treated in every known way,
But his spirochetes grow day by day;
He’s developed paresis,
Has long talks with Jesus,
And thinks he’s the Queen of the May.

Testing for tetanus is suggested whenever an individual has sustained a wound infection. Death usually results from spasms of the diaphragm and intercostal muscles. A second toxin tetanolysin, is a hemolysin that aids in tissue destruction.

Testing for tetanus is suggested whenever an individual has a history of wound infection and muscle stiffness. Prevention of tetanus involves the use of the tetanus toxoid. The toxoid, which incorporates an adjuvant (aluminum salts) to increase its immunizing potency, is given routinely with diphtheria toxoid and pertussis vaccine. An initial dose is normally administered a few months after birth, a second dose 4 to 6 months later, and finally a reinforcing dose 6 to 12 months after the second injection. A final booster is given between the ages of 4 to 6 years. For many years booster doses of tetanus toxoid were administered every 3 to 5 years. However, that practice has been discontinued since it has been shown that a single booster dose can provide protection for 10 to 20 years. Serious hypersensitivity reactions have occurred when too many doses of toxoid were administered over a period of years. Booster doses today are generally given only when an individual has sustained a wound infection.

Control measures for tetanus are not possible because of the wide dissemination of the bacterium in the soil and the long survival of its endospores. The case fatality rate in generalized tetanus ranges from 30 to 90% because tetanus treatment is not very effective. Therefore prevention is all important and depends on (1) active immunization with toxoid, (2) proper care of wounds contaminated with soil, (3) prophylactic use of antitoxin, and (4) administration of penicillin. Around 100 cases of tetanus are reported annually in the United States—the majority of which are intravenous drug users.

Trachoma

Trachoma [Greek trachoma, roughness] is a contagious disease created by Chlamydia trachomatis serotypes A–C. It is one of the oldest known infectious diseases of humans and is the greatest single cause of blindness throughout the world. Probably over 500 million people are infected and 20 million blinded each year by this chlamydia. In endemic areas most children are chronically infected within a few years of birth. Active disease in adults over age 20 is three times as frequent in females as in males because...
of mother-child contact. Although uncommon in the United States, except among American Indians in the Southwest, trachoma is widespread in Asia, Africa, and South America.

Trachoma is transmitted by contact with inanimate objects such as soap and towels, by hand-to-hand contact that carries *C. trachomatis* from an infected eye to an uninfected eye, or by flies. The disease begins abruptly with an inflamed conjunctiva. This leads to an inflammatory cell exudate and necrotic eyelash follicles (figure 39.22). The disease usually heals spontaneously. However, with reinfection, vascularization of the cornea, or pan-
nus formation, occurs, leading to scarring of the conjunctiva. If scar tissue accumulates over the cornea, blindness results.

Diagnosis and treatment of trachoma are the same as for inclusion conjunctivitis (previously discussed). However, prevention and control of trachoma lies more in health education and personal hygiene—such as access to clean water for washing—than in treatment.

### Tularemia

The gram-negative bacterium *Francisella tularensis* subsp. *tularensis* (Jellison type A) is widely found in animal reservoirs in the United States and causes the disease *tularemia* (from Tulare, a county in California where the disease was first described). It may be transmitted to humans by biting arthropods (ticks, deer flies, or mosquitoes), direct contact with infected tissue (rabbits), inhalation of aerosolized bacteria, or ingestion of contaminated food or water. After an incubation period of 2 to 10 days, a primary ulcerative lesion appears at the infection site, lymph nodes enlarge, and a high fever develops. Diagnosis is by PCR or culture of the bacterium and fluorescent antibody and agglutination tests; treatment is with streptomycin, tetracycline, or aminoglycoside antibiotics. Prevention and control involves public education, protective clothing, and vector control. An attenuated live vaccine is available from the United States Army for high-risk laboratory workers. Fewer than 300 cases of tularemia are reported annually in the United States.

### Sexually Transmitted Diseases

Sexually transmitted diseases (STDs) represent a worldwide public health problem. The various viruses that cause STDs are presented in chapter 38, the responsible bacteria in chapter 39, and the yeasts and protozoa in chapter 40. Table 39.4 lists the various microorganisms that can be sexually transmitted and the diseases they cause.

The spread of most sexually transmitted diseases is currently out of control. In the United States alone, at least 8 to 10 million persons contract some type of STD each year. Some of the STDs that are prevalent in the United States are gonorrhea, syphilis, genital herpes, chlamydial infections, trichomoniasis, hepatitis B, and the most serious of all because of its high mortality, AIDS.

STDs were formerly called venereal diseases (from Venus, the Roman goddess of love). They occur most frequently in the most sexually active age group—15 to 30 years of age—but anyone who has sexual contact with an infected individual is a potential victim. In general, the more sexual partners a person has, the more likely that the person is to acquire an STD.

As noted in previous chapters, some of the microorganisms that cause STDs can also be transmitted by nonsexual means. Examples include transmission by contaminated hypodermic needles and syringes shared among intravenous drug users, contaminated blood transfusions, and infected mothers to their infants.

Some STDs can be cured quite easily, but others, especially those caused by viruses, are presently difficult or impossible to cure. Because treatments are often inadequate, prevention is essential. Preventive measures are based mainly on better education of the total population and when possible, control of the sources of infection and treatment of infected individuals with chemotherapeutic agents.

1. Describe the three phases of lymphogranuloma venereum.
2. Describe several diseases caused by the staphylococci.
3. How does *C. trachomatis*, serotypes A–C, cause trachoma? Describe how it is transmitted, and the way in which blindness may result.
4. What is nongonococcal urethritis and what agents can cause it? Describe complications that may develop in the absence of treatment.
5. Name and describe the three stages of syphilis.
6. How is the disease tetanus acquired? What are its symptoms and how do they arise?
7. From what animal can tularemia be contracted?
8. Name four ways in which a person may contract an STD.

### 39.4 Food-Borne and Waterborne Diseases

Many microorganisms contaminating food and water can cause acute gastroenteritis or inflammation of the stomach and intestinal lining. When food is the source of the pathogen, the condition is often called *food poisoning*. Gastroenteritis can arise in two ways. The microorganisms may actually produce a food-
borne infection. That is, they may first colonize the gastrointestinal tract and grow within it, then either invade host tissues or secrete exotoxins. Alternatively the pathogen may secrete an exotoxin that contaminates the food and is then ingested by the host. This is sometimes referred to as a food intoxication because the toxin is ingested and the presence of living microorganisms is not required. Because these toxins disrupt the functioning of the intestinal mucosa they are called enterotoxins. Common symptoms of enterotoxin poisoning are nausea, vomiting, and diarrhea.

Worldwide, diarrheal diseases are second only to respiratory diseases as a cause of adult death; they are the leading cause of childhood death, and in some parts of the world they are responsible for more years of potential life lost than all other causes combined. For example, each year around 5 million children (more than 13,600 a day) die from diarrheal diseases in Asia, Africa, and South America. In the United States estimates exceed 10,000 deaths per year from diarrheal disease (pp. 973–76); Food spoilage (pp. 966–69); Waterborne diseases (pp. 987–91).

This section describes several of the more common bacteria associated with gastrointestinal infections, food intoxications, and waterborne diseases. Table 39.5 summarizes many of the bacterial pathogens responsible for food poisoning. The protozoa responsible for food- and waterborne diseases are covered in Chapter 40.
### Table 39.5  Bacteria That Cause Acute Bacterial Diarrheas and Food Poisonings

<table>
<thead>
<tr>
<th>Organism</th>
<th>Incubation Period (Hours)</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Fever</th>
<th>Epidemiology</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>1–8 (rarely, up to 18)</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td></td>
<td>Enterotoxins act on receptors in gut that transmit impulse to medullary centers; may also act as superantigens.</td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>2–16</td>
<td>+++</td>
<td>++</td>
<td>–</td>
<td></td>
<td>Enterotoxins formed in food or in gut from growth of <em>B. cereus</em>.</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>8–16</td>
<td>±</td>
<td>+++</td>
<td>–</td>
<td></td>
<td>Enterotoxin produced during sporulation in gut, causes hypersecretion.</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>18–24</td>
<td>±</td>
<td>Rare</td>
<td>–</td>
<td></td>
<td>Toxin absorbed from gut and blocks acetylcholine release at neuromuscular junction.</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (enterotoxigenic strain)</td>
<td>24–72</td>
<td>±</td>
<td>++</td>
<td>–</td>
<td></td>
<td>Organisms grow in gut and are a major cause of traveler’s diarrhea.</td>
</tr>
<tr>
<td><em>Vibrio parahaemolyticus</em></td>
<td>6–96</td>
<td>+</td>
<td>++</td>
<td>±</td>
<td></td>
<td>Toxin causes hypersecretion; vibrios invade epithelium; stools may be bloody.</td>
</tr>
<tr>
<td><em>Shigella</em> spp. (mild cases)</td>
<td>24–72</td>
<td>±</td>
<td>++</td>
<td>+</td>
<td></td>
<td>Organisms invade epithelial cells; blood, mucus, and neutrophils in stools. Infective dose &lt;10⁷ organisms.</td>
</tr>
<tr>
<td><em>Salmonella</em> spp. (gastroenteritis)</td>
<td>8–48</td>
<td>±</td>
<td>++</td>
<td>+</td>
<td></td>
<td>Superficial infection of gut, little invasion. Infective dose &gt;10⁷ organisms.</td>
</tr>
<tr>
<td><em>Salmonella typhi</em> (typhoid fever)</td>
<td>10–14 days</td>
<td>±</td>
<td>±</td>
<td>++</td>
<td></td>
<td>Symptoms probably due to endotoxins and tissue inflammation. Infective dose ≥10⁷ organisms.</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Days to weeks after antibiotic therapy</td>
<td>–</td>
<td>+++</td>
<td>+</td>
<td></td>
<td>Toxin causes epithelial necrosis in colon; pseudomembranous colitis.</td>
</tr>
<tr>
<td><em>Campylobacter jejuni</em></td>
<td>2–10 days</td>
<td>–</td>
<td>+++</td>
<td>++</td>
<td></td>
<td>Invasion of mucous membrane. Toxin production uncertain.</td>
</tr>
<tr>
<td><em>Yersinia enterocolitica</em></td>
<td>4–7 days</td>
<td>±</td>
<td>++</td>
<td>+</td>
<td></td>
<td>Gastroenteritis or mesenteric adenitis. Occasional bacteremia. Toxin produced occasionally.</td>
</tr>
</tbody>
</table>

Clinical Features

**Abrupt onset, intense vomiting for up to 24 hours, recovery in 24–48 hours. Occurs in persons eating the same food. No treatment usually necessary except to restore fluids and electrolytes.**

With incubation period of 2–8 hours, mainly vomiting. With incubation period of 8–16 hours, mainly diarrhea.

**Abrupt onset of profuse diarrhea; vomiting occasionally. Recovery usual without treatment in 1–4 days. Many clostridia in cultures of food and feces of patients.**

**Diplopia, dysphagia, dysphonia, difficulty breathing. Treatment requires clear airway, ventilation, and intravenous polyvalent antitoxin. Exotoxin present in food and serum. Mortality rate high.**

**Usually abrupt onset of diarrhea; vomiting rare. A serious infection in newborns. In adults, “traveler’s diarrhea” is usually self-limited in 1–3 days.**

**Abrupt onset of diarrhea in groups consuming the same food, especially crabs and other seafood. Recovery is usually complete in 1–3 days. Food and stool cultures are positive.**

**Abrupt onset of liquid diarrhea in endemic area. Needs prompt replacement of fluids and electrolytes IV or orally. Tetracyclines shorten excretion of vibrios. Stool cultures positive.**

**Abrupt onset of diarrhea, often with blood and pus in stools, cramps, tenesmus, and lethargy. Stool cultures are positive. Give trimethoprim sulfamethoxazole or ampicillin or chloramphenicol in severe cases. Do not give opiates. Often mild and self-limited. Restore fluids.**

**Gradual or abrupt onset of diarrhea and low-grade fever. Nausea, headache, and muscle aches common. No antimicrobials unless systemic dissemination is suspected. Stool cultures are positive. Prolonged carriage is frequent.**

**Initially fever, headache, malaise, anorexia, and muscle pains. Fever may reach 40°C by the end of the first week of illness and lasts for 2 or more weeks. Diarrhea often occurs, and abdominal pain, cough, and sore throat may be prominent. Antibiotic therapy shortens duration of the illness.**

**Especially after abdominal surgery, abrupt bloody diarrhea and fever. Toxins in stool. Oral vancomycin useful in therapy.**

**Fever, diarrhea; PMNs and fresh blood in stool, especially in children. Usually self-limited. Special media needed for culture at 43°C. Erythromycin in severe cases with invasion. Usually recovery in 5–8 days.**

**Severe abdominal pain, diarrhea, fever; PMNs and blood in stool; polyarthritis, erythema nodosum, especially in children. If severe, treat with gentamicin. Keep stool specimen at 4°C before culture.**

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**Botulism**

Food-borne botulism [Latin *botulus*, sausage] is a form of food poisoning caused by *Clostridium botulinum*, which is an obligately anaerobic endospore-forming, gram-positive rod that is found in soil and aquatic sediments. The most common source of infection is home-canned food that has not been heated sufficiently to kill contaminating *C. botulinum* endospores. The endospores can germinate, and a toxin is produced during vegetative growth. If the food is then eaten without adequate cooking, the toxin remains active and the disease results.

The botulimum toxin is a neurotoxin that binds to the synapses of motor neurons. It selectively cleaves the synaptic vesicle membrane protein synaptobrevin, thus preventing exocytosis and release of the neurotransmitter acetylcholine. As a consequence, muscles do not contract in response to motor neuron activity, and flaccid paralysis results (Box 39.6). Symptoms of botulism occur within 18 to 24 hours of toxin ingestion and include blurred vision, difficulty in swallowing and speaking, muscle weakness, nausea, and vomiting. Without adequate treatment, 1/3 of the patients may die within a few days of either respiratory or cardiac failure.

Laboratory diagnosis is by a hemagglutination test or inoculation of mice with the patient’s serum, stools, or vomitus to prove toxigenicity. Treatment relies on supportive care and polyvalent antitoxin. Fewer than 100 cases of botulism occur in the United States annually.

Infant botulism is the most common form of botulism in the United States and is confined to infants under a year of age. Approximately 100 cases are reported each year. It appears that ingested endospores, which may be naturally present in honey or house dust, germinate in the infant’s intestine. *C. botulinum* then multiplies and produces the toxin. The infant becomes constipated, listless, generally weak, and eats poorly. Death may result from respiratory failure.

Prevention and control of botulism involves (1) strict adherence to safe food-processing practices by the food industry, (2) educating the public on safe home-preserving (canning) methods for foods, and (3) not feeding honey to infants younger than 1 year of age.

**Campylobacter jejuni Gastroenteritis**

*Campylobacter jejuni* is a gram-negative curved rod found in the intestinal tract of animals. Studies with chickens, turkeys, and cattle have shown that as much as 50 to 100% of a flock or herd of these birds or animals secrete *C. jejuni*. These bacteria also can be isolated in high numbers from surface waters. They are transmitted to humans by contaminated food and water, contact with infected animals, or anal-oral sexual activity. *C. jejuni* causes an estimated 2 million cases of *Campylobacter* gastroenteritis—inflammation of the intestine—or campylobacteriosis and subsequent diarrhea in the United States each year.

The incubation period is 2 to 10 days. *C. jejuni* invades the epithelium of the small intestine, causing inflammation, and also secretes an exotoxin that is antigenically similar to the cholera...
Food poisoning, and the treatment of cancer and other diseases. For example, research is underway to use clostridial toxins or toxin domains for drug delivery, prevention of food poisoning, and the treatment of cancer and other diseases. The remarkable success of botulinum toxin as a therapeutic agent has thus created a new field of investigation in microbiology.

### Clostridial Toxins as Therapeutic Agents: Benefits of Nature’s Most Toxic Proteins

Some toxins are currently being used for the treatment of human disease. Specifically, botulinum toxin, the most poisonous biological substance known, is being used for the treatment of specific neuromuscular disorders characterized by involuntary muscle contractions. Since approval of type-A botulinum toxin by the FDA in 1989 for three disorders (strabismus [crossing of the eyes], blepharospasm [spasmodic contractions of the eye muscles], and hemifacial spasm [contractions of one side of the face]), the number of neuromuscular problems being treated has increased to include other tremors, cosmetic applications, migraines, and tension headaches, and other maladies. The remarkable therapeutic utility of botulinum toxin lies in its ability to specifically and potently inhibit involuntary muscle activity for an extended duration. Overall, the clostridia (currently one of the largest and most diverse genera of bacteria containing about 130 “official” species) produce more protein toxins than any other bacterial genus and are a rich reservoir of toxins for research and medicinal uses. For example, research is underway to use clostridial toxins or toxin domains for drug delivery, prevention of food poisoning, and the treatment of cancer and other diseases. The remarkable success of botulinum toxin as a therapeutic agent has thus created a new field of investigation in microbiology.

### Cholera

Throughout recorded history cholera [Greek cholē, bile] has caused seven pandemics in various areas of the world, especially in Asia, the Middle East, and Africa. The disease has been rare in the United States since the 1800s, but an endemic focus is believed to exist on the gulf coast of Louisiana and Texas.

Cholera is caused by the gram-negative *Vibrio cholerae* bacterium of the family *Vibrionaceae* (figure 39.23). Although there are many serogroups, only O1 and O139 have exhibited the ability to cause epidemics. *V. cholerae* O1 is divided into two serotypes, Inaba and Ogawa, and two biotypes, classic and El Tor.

Cholera is acquired by ingesting food or water contaminated by fecal material from patients or carriers. (Shelfish and copepods are natural reservoirs.) In 1961 the El Tor biotype emerged as an important cause of cholera pandemics, and in 1992 the newly identified strain *V. cholerae* O139 emerged in Asia. This novel toxigenic strain does not agglutinate with O1 antiserum but possesses epidemic and pandemic potential. In Calcutta, India, serogroup O139 of *V. cholerae* has displaced El Tor *V. cholerae* serogroup O1 (causative agent of the seventh pandemic), an event that has never happened in the recorded history of cholera.

Once the bacteria enter the body, the incubation period is from 24 to 72 hours. The bacteria adhere to the intestinal mucosa of the small intestine, where they are not invasive but secrete cholera toxin, a cholera toxin. Choleragen is a protein composed of two functional units, an enzymatic A subunit and an intestinal receptor-binding B subunit. The A subunit enters the intestinal epithelial cells and activates the enzyme adenylate cyclase by the addition of an ADP-ribosyl group in a way similar to that employed by diphtheria toxin (see figure 34.5b). As a result choleragen stimulates hypersecretion of water and chloride ions while inhibiting absorption of sodium ions. The patient loses massive quantities of fluid and electrolytes, which is associated with abdominal muscle cramps, vomiting, fever, and watery diarrhea. The diarrhea can be so profuse that a person can lose 10 to 15 liters of fluid during the infection. Death may result from the elevated concentration of blood proteins, caused by reduced fluid levels, which leads to circulatory shock and collapse. There is now evidence that the cholera toxin gene is carried by the CTX filamentous bacteriophage. The phage binds to the pilus used to
colonize the host’s gut, enters the bacterium, and incorporates its genes into the bacterial chromosome.

Laboratory diagnosis is by culture of the bacterium from feces and subsequent identification by agglutination reactions with specific antisera. Treatment is by oral rehydration therapy with NaCl plus glucose to stimulate water uptake by the intestine; the antibiotics of choice are a tetracycline, trimethoprim-sulfamethoxazole, or ciprofloxacin. The most reliable control methods are based on proper sanitation, especially of water supplies. The mortality rate without treatment is often over 50%; with treatment and supportive care, it is less than 1%. Fewer than 20 cases of cholera are reported each year in the United States.

Listeria

*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 immunosuppression caused by illness or medication. Recent evidence suggests that a substantial number of cases of human *listeriosis* are attributable to the food-borne transmission of *L. monocytogenes*. *Listeria* outbreaks have been traced to sources such as contaminated milk, soft cheeses, vegetables, and meat. Unlike many of the food-borne pathogens, which cause primarily gastrointestinal illness, *L. monocytogenes* causes invasive syndromes such as meningitis, sepsis, and stillbirth.

*L. monocytogenes* is an intracellular pathogen, a characteristic consistent with its predilection for causing illness in persons with deficient cell-mediated immunity. This bacterium can be found as part of the normal gastrointestinal microbiota in healthy individuals. In immunosuppressed individuals, invasion, intracellular multiplication, and cell-to-cell spread of the bacterium appears to be mediated through proteins such as internalin, the helical multiplication, and cell-to-cell spread of the bacterium associated with pregnancy. For example, local immunosuppression at the maternal-fetal interface of the placenta may facilitate intrauterine infection following transient maternal bacteremia.

Diagnosis of listeriosis is by culture of the bacterium. Treatment is intravenous administration of either ampicillin or penicillin. Since *L. monocytogenes* is frequently isolated from food, the USDA (the U.S. Department of Agriculture) and manufacturers are pursuing measures to reduce the contamination of food products by this bacterium.

Salmonellosis

*Salmonella* (*Salmonella gastroenteritis*) is caused by over 2,000 *Salmonella* serovars (strains; a subspecies category). The most frequently reported one from humans is *S. serovar typhimurium*. This bacterium is a gram-negative, motile, non-spore-forming rod.

The initial source of the bacterium is the intestinal tracts of birds and other animals. Humans acquire the bacteria from contaminated foods such as beef products, poultry, eggs, egg products, or water. Around 45,000 cases a year are reported in the United States, but there actually may be as many as 2 to 3 million cases annually.

Once the bacteria are in the body, the incubation time is only about 8 to 48 hours. The disease results from a true food-borne infection because the bacteria multiply and invade the intestinal mucosa where they produce an enterotoxin and cytoxin that destroy the epithelial cells. Abdominal pain, cramps, diarrhea, nausea, vomiting, and fever are the most prominent symptoms, which usually persist for 2 to 5 days but can last for several weeks. During the acute phase of the disease, as many as 1 billion salmonella can be found per gram of feces. Most adult patients recover, but the loss of fluids can cause problems for children and elderly people.

Laboratory diagnosis is by isolation of the bacterium from food or patients’ stools. Treatment is with fluid and electrolyte replacement. Prevention depends on good food-processing practices, proper refrigeration, and adequate cooking.

Shigellosis

*Shigellosis* or bacillary dysentery is a diarrheal illness resulting from an acute inflammatory reaction of the intestinal tract caused by the four species of the genus *Shigella* (gram-negative, non-motile, facultative rods). About 25,000 to 30,000 cases a year are reported in the United States, and around 600,000 deaths a year worldwide are due to bacillary dysentery.

*Shigella* is restricted to human hosts. *S. sonnei* is the usual pathogen in the United States and Britain, but *S. flexneri* is also fairly common. The organism is transmitted by the fecal-oral route—primarily by food, fingers, feces, and flies (the four “F’s”)—and is most prevalent among children, especially 1- to 4-year-olds. The infectious dose is only around 10 to 100 bacteria. In the United States shigellosis is a particular problem in day care centers and custodial institutions where there is crowding.

The shigelae are facultative intracellular parasites that multiply within the cells of the colon epithelium. The bacteria induce the mucosal cell to phagocytose them and then disrupt the phagosome membrane. After reproducing in the cytoplasmic matrix, the shigellae invade adjacent mucosal cells. They may produce both endotoxins and exotoxins but do not usually spread beyond the colon epithelium. The watery stools often contain blood, mucus, and pus. In severe cases the colon can become ulcerated.

The incubation period usually ranges from 1 to 3 days and the organisms are shed over a period of 1 to 2 weeks. Identification of isolates is based on biochemical characteristics and serology. The disease normally is self-limiting in adults and lasts an average of 4 to 7 days; in infants and young children it may be fatal. Usually fluid and electrolyte replacement are sufficient, and antibiotics may not be required in mild cases although they can shorten the duration of symptoms. Sometimes, particularly in malnourished infants and children, neurological complications and kidney failure result. When necessary, treatment is with trimethoprim-sulfamethoxazole or fluoroquinolones. Antibiotic-resistant strains are becoming a problem. Prevention is a matter of good personal hygiene and the maintenance of a clean water supply.
Staphylococcal Food Poisoning

Staphylococcal food poisoning is the major type of food intoxication in the United States. It is caused by ingestion of improperly stored or cooked food (particularly foods such as ham, processed meats, chicken salad, pastries, ice cream, and hollandaise sauce) in which *Staphylococcus aureus* has grown.

*S. aureus* (a gram-positive coccus) is very resistant to heat, drying, and radiation; it is found in the nasal passages and on the skin of humans and other mammals worldwide. From these sources it can readily enter food. If the bacteria are allowed to incubate in certain foods, they produce heat-stable enterotoxins that render the food dangerous even though it appears normal. Once the bacteria have produced the toxin, the food can be extensively and properly cooked, killing the bacteria but without destroying the toxin. Intoxication can therefore result from food that has been thoroughly cooked. Six different enterotoxins have been identified and are designated A, B, C1, C2, D, and E. These toxins appear to act as neurotoxins that stimulate vomiting through the vagus nerve. At least some are superantigens and trigger the release of IL-2 and other lymphokines.

Typical symptoms include severe abdominal pain, cramps, diarrhea, vomiting, and nausea. The onset of symptoms is rapid (usually 1 to 8 hours) and of short duration (usually less than 24 hours). The mortality rate of staphylococcal food poisoning is negligible among healthy individuals.

Diagnosis is based on the symptoms or laboratory diagnosis of the bacteria from foods. Enterotoxins may be detected in foods by animal toxicity tests. Treatment is with fluid and electrolyte replacement. Prevention and control involve avoidance of food contamination, and control of personnel responsible for food preparation and distribution.

Traveler’s Diarrhea and *Escherichia coli* Infections

Millions of people travel yearly from country to country (see section 37.11). Unfortunately a large percentage of these travelers acquire a rapidly acting, dehydrating condition called traveler’s diarrhea. This diarrhea results from an encounter with certain viruses, bacteria, or protozoa usually absent from the traveler’s environment. One of the major causative agents is *E. coli*. This bacterium circulates in the resident population, typically without causing symptoms due to the immunity afforded by previous exposure. Because many of these bacteria are needed to initiate infection, contaminated food and water are the major means by which the bacteria are spread. This is the basis for the popular warnings to international travelers: “Don’t drink the local water” and “Boil it, peel it, cook it, or forget it.”

*E. coli* may cause diarrheal disease by several mechanisms, and six categories or strains of diarrheagenic *E. coli* are now recognized: enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enterohemorrhagic *E. coli* (EHEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), and diffusely adhering *E. coli* (DAEC).

The enterotoxigenic *E. coli* (ETEC) strains produce one or both of two distinct enterotoxins (see Box 13.1), which are responsible for the diarrhea and distinguished by their heat stability: heat-stable enterotoxin (ST) and heat-labile enterotoxin (LT). The genes for ST and LT production and for colonization factors are usually plasmid-borne and acquired by horizontal gene transfer. ST binds to a glycoprotein receptor that is coupled to guanylate cyclase on the surface of intestinal epithelial cells. Activation of guanylate cyclase stimulates the production of cyclic guanosine monophosphate (cGMP), which leads to the secretion of electrolytes and water into the lumen of the small intestine, manifested as the watery diarrhea characteristic of an ETEC infection. LT binds to specific gangliosides on the epithelial cells and activates membrane-bound adenylyl cyclase, which leads to increased production of cyclic adenosine monophosphate (cAMP) through the same mechanism employed by cholera toxin. Again, the result is hypersecretion of electrolytes and water into the intestinal lumen.

The enteroinvasive *E. coli* (EIEC) strains cause diarrhea by penetrating and multiplying within the intestinal epithelial cells. The ability to invade the epithelial cells is associated with the presence of a large plasmid; EIEC may also produce a cytotoxin and an enterotoxin.

The enteropathogenic *E. coli* (EPEC) strains attach to the brush border of intestinal epithelial cells and cause a specific type of cell damage called effacing lesions. Effacing lesions or attaching-effacing (AE) lesions represent destruction of brush border microvilli adjacent to adhering bacteria. This cell destruction leads to the subsequent diarrhea. As a result of this pathology, the term AE *E. coli* is used to describe true EPEC strains. It is now known that AE *E. coli* is an important cause of diarrhea in children residing in developing countries.

The enterohemorrhagic *E. coli* (EHEC) strains carry the genetic determinants for attaching-effacing lesions and Shigella-like toxin production. The attaching-effacing lesion causes hemorrhagic colitis with severe abdominal pain and cramps followed by bloody diarrhea. The Shiga-like toxins I and II (also called verotoxins 1 and 2) have also been implicated in two extraintestinal diseases: *hemolytic uremic syndrome* and thrombotic thrombocytopenic purpura. It is believed these toxins kill vascular endothelial cells. A major form of EHEC is the *E. coli* O157:H7 that has caused many outbreaks of hemorrhagic colitis in the United States since it was first recognized in 1982. Currently there are a minimum of 20,000 *E. coli* O157:H7 cases and 250 deaths in the United States each year.

The enteroaggregative *E. coli* (EAEC) strains adhere to epithelial cells in localized regions, forming clumps of bacteria with a “stacked brick” appearance. Conventional extracellular toxins have not been detected in EAEC, but unique lesions are seen in epithelial cells, suggesting the involvement of toxins.

The diffusely adhering *E. coli* (DAEC) strains adhere over the entire surface of epithelial cells and usually cause disease in immunologically naive or malnourished children. It has been suggested that DAEC may have an as yet undefined virulence factor.

Diagnosis of traveler’s diarrhea caused by *E. coli* is based on past travel history and symptoms. Laboratory diagnosis is by isolation of the specific type of *E. coli* from feces and identification...
using DNA probes, the determination of virulence factors, and the polymerase chain reaction. Treatment is with fluid and electrolytes plus doxycycline and trimethoprim-sulfamethoxazole. Recovery is usually without complications. Prevention and control involve avoiding contaminated food and water.

**Typhoid Fever**

Typhoid [Greek typhodes, smoke] fever is caused by several virulent serovars of *Salmonella typhi* and is acquired by ingestion of food or water contaminated by feces of infected humans or animals. In earlier centuries the disease occurred in great epidemics.

Once in the small intestine the incubation period is about 10 to 14 days. The bacteria colonize the small intestine, penetrate the epithelium, and spread to the lymphoid tissue, blood, liver, and gallbladder. Symptoms include fever, headache, abdominal pain, anorexia, and malaise, which last several weeks. After approximately 3 months, most individuals stop shedding bacteria in their feces. However, a few individuals continue to shed *S. typhi* for extended periods but show no symptoms. In these carriers, the bacteria continue to grow in the gallbladder and reach the intestine through the bile duct (see Box 37.2 on “Typhoid Mary,” one of the most famous typhoid carriers).

Laboratory diagnosis of typhoid fever is by demonstration of typhoid bacilli in the blood, urine, or stools and serology (the Widal test). Treatment with ceftriaxone, trimethoprim-sulfamethoxazole, or ampicillin has reduced the mortality rate to less than 1%. Recovery from typhoid confers a permanent immunity. Purification of drinking water, milk pasteurization, prevention of food handling by carriers, and complete isolation of patients are the most successful prophylactic measures. There is a vaccine for high-risk individuals (see table 33.1). About 400 to 500 cases of typhoid fever occur annually in the United States.

1. Distinguish between food intoxication, food poisoning, and food borne infection. What is an enterotoxin?
2. Why is cholera the most severe form of gastroenteritis?
3. How does one acquire botulism? Describe how botulinum toxin causes flaccid paralysis.
4. What is the most common form of gastroenteritis in the United States and how are the symptoms caused?
5. What is a common source of *Listeria* infections? How is the intracellular growth of *Listeria* related to the symptoms it produces and the observation that immunocompromised individuals are most at risk?
6. What is the usual source of the bacterium responsible for salmonellosis? Shigellosis? Where and how does Shigella infect people?
7. Describe the most common type of food intoxication in the United States and how it arises.
8. Describe a typhoid carrier. How does one become a carrier?
9. What are some specific causes of traveler’s diarrhea? Briefly describe the six major types of pathogenic *E. coli*.

### 39.5 Sepsis and Septic Shock

Some microbial diseases and their effects cannot be categorized under a specific mode of transmission. Two important examples are sepsis and septic shock. Septic shock is the most common cause of death in intensive care units and the thirteenth most common cause of death in the United States. Unfortunately the incidence of these two disorders continues to rise: 400,000 cases of sepsis and 200,000 episodes of septic shock are estimated to occur annually in the United States, resulting in more than 100,000 deaths.

**Sepsis** recently has been redefined by physicians as the systemic response to a microbial infection (see also table 34.2). This response is manifested by two or more of the following conditions: temperature above 38 or below 36°C; heart rate above 90 beats per minute; respiratory rate above 20 breaths per minute or a pCO2 below 32 mmHg; leukocyte count above 12,000 cells per ml or below 4,000 cells per ml. **Septic shock** is sepsis associated with severe hypotension (low blood pressure due to shock) despite adequate fluid replacement. Gram-positive bacteria, fungi, and endotoxin-containing gram-negative bacteria can initiate the pathogenic cascade of sepsis leading to septic shock. Gram-negative sepsis is most commonly caused by *Escherichia coli*, followed by *Klebsiella spp.*, *Enterobacter spp.*, and *Pseudomonas aeruginosa*. Endotoxin, or lipopolysaccharide (LPS; see figure 3.25), an integral component of the outer membrane of gram-negative bacteria, has been implicated as a primary initiator of the pathogenesis of gram-negative septic shock.

The pathogenesis of sepsis and septic shock begins with the proliferation of the microorganism at the location of infection (figure 39.24). The microorganism may invade the bloodstream directly or may proliferate locally and release various products into the bloodstream. These products include both structural components of the microorganisms (endotoxin, teichoic acid antigen) and exotoxins synthesized by the microorganism. All of these products can stimulate the release of the endogenous mediators of sepsis from endothelial cells, plasma cells (monocytes, macrophages, neutrophils), and plasma cell precursors.

The endogenous mediators have profound physiological effects on the heart, vasculature, and other body organs. The consequences are either recovery or septic shock leading to death. Death usually ensues if one or more organ systems fail completely.

### 39.6 Dental Infections

Some microorganisms found in the oral cavity are discussed in section 31.2 and presented in figure 31.2. Of this large number, only a few bacteria can be considered true dental pathogens or odontopathogens. These few odontopathogens are responsible for the most common bacterial diseases in humans: tooth decay and periodontal disease.

**Dental Plaque**

The human tooth has a natural defense mechanism against bacterial colonization that complements the protective role of saliva. The hard enamel surface selectively absorbs acidic glycoproteins (mucins)
from saliva, forming a membranous layer called the **acquired enamel pellicle**. This pellicle, or organic covering, contains many sulfate ($SO_4^{2-}$) and carboxylate ($—COO^-\$) groups that confer a net negative charge to the tooth surface. Because most bacteria also have a net negative charge, there is a natural repulsion between the tooth surface and bacteria in the oral cavity. Unfortunately this natural defense mechanism breaks down when dental plaque formation occurs.

**Dental plaque** formation begins with the initial colonization of the pellicle by *Streptococcus gordonii*, *S. oralis*, and *S. mitis*. These bacteria selectively adhere to the pellicle by specific ionic, hydrophobic, and lectinlike interactions. Once the tooth surface is colonized, subsequent attachment of other bacteria results from a variety of specific coaggregation reactions (figure 39.25a,b). **Coaggregation** is the result of cell-to-cell recognition between genetically distinct bacteria. Many of these interactions are mediated by a lectin on one bacterium that interacts with a complementary carbohydrate receptor on the other bacterium. The most important species at this stage are *Actinomyces viscosus*, *A. naeslundii*, and *S. gordonii*. After these species colonize the pellicle, a microenvironment is created that allows *Streptococcus mutans* and *S. sobrinus* to become established on the tooth surface by attaching to these initial colonizers. Biofilms (pp. 620–22)

These streptococci produce extracellular enzymes (glucosyltransferases) that polymerize the glucose moiety of sucrose into a
Figure 39.25  The Formation of Dental Plaque on a Freshly Cleaned Tooth Surface. (a) Diagrammatic representation of the proposed temporal relationship of bacterial accumulation and multigenic coaggregation during the formation of dental plaque on the acquired enamel pellicle. Early colonizers of the tooth surface coaggregate with each other, and late colonizers of the tooth surface coaggregate with each other. With a few exceptions, early colonizers do not recognize late colonizers. After the tooth surface is covered with the earliest colonizers, each newly added bacterium becomes a new surface for recognition by unattached bacteria. (b) Dental plaque consisting of bacteria plus polysaccharides such as glucan is shown attached to the enamel surface of a tooth; transmission electron micrograph (×13,600). (c) The enzyme glucosyltransferase or dextranuclase (produced by the oral bacteria) cause the assembly of glucose units from sucrose into glucans, and fructose is released. Sucrose, glucose, and fructose molecules also are metabolized by the oral bacteria to produce lactate and other acids. Lactate is responsible for dental cavities.
heterogeneous group of extracellular water-soluble and water-insoluble glucan polymers and other polysaccharides. The fructose by-product can be used in fermentation. **Glucans** are branched-chain polysaccharides composed of glucose units; many glucans synthesized by oral streptococci have glucose held together by \( \alpha(1 \rightarrow 6) \) and \( \alpha(1 \rightarrow 3) \) linkages (figure 39.25c). They act like a cement to bind bacterial cells together, forming a plaque ecosystem. (Dental plaque is one of the most dense collections of bacteria in the body—and perhaps the source of the first human microorganisms to be seen under a microscope by Anton van Leeuwenhoek in the seventeenth century.) Once plaque becomes established, a low oxidation reduction potential is created on the surface of the tooth. This leads to the growth of strict anaerobic bacteria (*Bacteroides melaninogenicus, B. oralis, and Veillonella alcalescens*), especially between opposing teeth and the dental-gingival crevices.

After the microbial plaque ecosystem develops, bacteria produce lactic and possibly acetic and formic acids from sucrose and other sugars. Because plaque is not permeable to saliva, the acids are not diluted or neutralized, and they demineralize the enamel to produce a lesion on the tooth. It is this chemical lesion that initiates dental decay.

**Dental Decay (Caries)**

As described previously, a histologically undetectable chemical lesion caused by the diffusion into the tooth’s enamel of undisassociated fermentation acids initiates the decay process. Once these acids move below the enamel surface, they dissociate and react with the hydroxyapatite of the enamel to form soluble calcium and phosphate ions. As the ions diffuse outward, some reprecipitate as calcium phosphate salts in the tooth’s surface layer to create a histologically sound outer layer overlying a porous subsurface area. Between meals and snacks, the pH returns to neutrality and some calcium phosphate reenters the lesion and crystallizes. The result is a demineralization-remineralization cycle.

When fermentable foods high in sucrose are eaten for prolonged periods, acid production overwhelms the repair process and demineralization is greater than remineralization. This leads to dental decay or caries [Latin, rottenness]. Once the hard enamel has been breached, bacteria can invade the dentin and pulp of the tooth and cause its death.

No drugs are available to prevent dental caries. The main strategies for prevention include minimal ingestion of sucrose; daily brushing, flossing, and mouthwashes; and professional cleaning at least twice a year to remove plaque. The use of fluorides in toothpaste, drinking water, mouthwashes, or professionally applied to the teeth protects against lactic and acetic acids and reduces tooth decay.

**Periodontal Disease**

**Periodontal disease** refers to a diverse group of diseases that affect the periodontium. The **periodontium** is the supporting structure of a tooth and includes the cementum, the periodontal membrane, the bones of the jaw, and the gingivae (gums). The gingiva is dense fibrous tissue and its overlying mucous mem-

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**Figure 39.26 Periodontal Disease.** Notice the plaque on the teeth (arrow), especially at the gingival (gum) margins, and the inflamed gingiva.

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**1.** Name some common odontopathogens that are responsible for dental caries, dental plaque, and periodontal disease. Be specific.

**2.** What is the function of the acquired enamel pellicle?

**3.** How does plaque formation occur? Dental decay?

**4.** Describe some pathological manifestations of periodontal disease.

**5.** How can caries and periodontal diseases be prevented?
Summary

1. Although only a small percentage of all bacteria are responsible for human illness, the suffering and death they cause are significant. Each year, millions of people are infected by pathogenic bacteria using the four major modes of transmission: airborne, arthropod-borne, direct contact, and food-borne and waterborne.

2. As the fields of microbiology, immunology, pathology, pharmacology, and epidemiology have expanded current understanding of the disease process, the incidence of many human illnesses has decreased. Many bacterial infections, once the leading cause of death, have been successfully brought under control in most developed countries. Alternatively, several are increasing in incidence throughout the world.

3. The bacteria emphasized in this chapter and the diseases they cause are as follows:
   a. Airborne diseases
     - diphtheria (Corynebacterium diphtheriae) (figure 39.1)
     - Legionnaires’ disease and Pontiac fever (Legionella pneumophila)
     - meningitis (Haemophilus influenzae type b, Neisseria meningitidis, and Streptococcus pneumoniae)
     - M. avium-M. intracellulare pneumonia
     - Streptococcal diseases (Streptococcus pyogenes) (figure 39.3)
     - tuberculosis (Mycobacterium tuberculosis) (figure 39.7)
     - pertussis (Bordetella pertussis)
   b. Arthropod-borne diseases
     - ehrlichiosis (Ehrlichia chaffeensis)
     - epidemic (louse-borne) typhus (Rickettsia prowazekii)
   c. Direct contact diseases
     - anthrax (Bacillus anthracis)
     - bacterial vaginosis (Gardnerella vaginalis)
     - cat-scratch disease (Bartonella henselae)
     - chancroid (Haemophilus ducreyi)
     - chlamydial pneumonia (Chlamydia pneumoniae)
     - gas gangrene or clostridial myonecrosis (Clostridium perfringens)
     - genitourinary mycoplasmal diseases (Ureaplasma urealyticum, Mycoplasma hominis)
     - gonorrhea (Neisseria gonorrhoeae) inclusion conjunctivitis (Chlamydia trachomatis)
     - leprosy (Mycobacterium leprae)
     - lymphogranuloma venereum (Chlamydia trachomatis)
     - mycoplasmal pneumonia (Mycoplasma pneumoniae)
     - nongonococcal urethritis (various microorganisms)
     - peptic ulcer disease (Helicobacter pylori)
     - psittacosis (ornithosis) (Chlamydia psittaci)
     - staphylococcal diseases (Staphylococcus aureus) (figure 39.18)
     - syphilis (Treponema pallidum)
     - tetanus (Clostridium tetani)

4. Gram-positive bacteria, fungi, and endotoxin-containing gram-negative bacteria can initiate the pathogenic cascade of sepsis leading to septic shock (figure 39.24). Gram-negative sepsis is most commonly caused by E. coli, followed by Klebsiella spp., Enterobacter spp., and Pseudomonas aeruginosa.

5. Dental plaque formation begins on a tooth with the initial colonization of the acquired enamel pellicle by Streptococcus gordonii, S. oralis, and S. mitis. Other bacteria then become attached and form a plaque ecosystem (figure 39.25). The bacteria produce acids that cause a chemical lesion on the tooth and initiate dental decay or caries. Periodontal disease is a group of diverse clinical entities that affect the periodontium. Disease is initiated by the formation of subgingival plaque, which leads to tissue inflammation known as periodontitis and to periodontal pockets. Bacteria that colonize these pockets can cause an abscess, periodontosis, gingivitis, and general tissue necrosis.

Key Terms

- acquired enamel pellicle
- anthrax
- aseptic meningitis syndrome
- bacterial (septic) meningitis
- bacterial vaginosis
- biofilm
- Bright’s disease
- buboes
- bubonic plague
- campylobacteriosis
- caries
- caseous lesion
- cat-scratch disease (CSD)
- cellulitis
- chancroid
- chlamydial pneumonia
- cholera
- choleragen
- clostridial myonecrosis
- clue cells
- coaggregation
- congenital syphilis
- cutaneous anthrax
- cutaneous diphtheria
- dental plaque
- diffusely adhering E. coli (DAEC)
- diphtheria
- DPT vaccine
- effacing lesions
- ehrlichiosis
- endemic (murine) typhus
- endogenous infection
- enteraggregative E. coli (EAagEC)
- enterohemorrhagic E. coli (EHEC)
- enteroinvasive E. coli (EIEC)
- enteropathogenic E. coli (EPEC)
- enterotoxigenic E. coli (ETEC)
- enterotoxin
- epidemic (louse-borne) typhus
- erysipelas
- eschar
- exfoliative toxin (exfoliatin)
- food-borne infection
- food intoxication
- food poisoning
- gas gangrene
- gastritis
- gastroenteritis
- gastrointestinal anthrax
- genital ulcer disease
- Ghon complex
- gingivitis
- K. pneumoniae
- lymphogranuloma venereum
- meningococcemia
- meningococcal septicaemia
- meningococcal meningitis
- meningococcal meningococcemia
Questions for Thought and Review

1. Briefly describe each of the major or most common bacterial diseases in terms of its causative agent, signs and symptoms, the course of infection, mechanism of pathogenesis, epidemiology, and prevention and/or treatment.
2. Because there are many etiologies of gastroenteritis, how is a definitive diagnosis usually made?
3. Differentiate between the following factors of bacterial intoxication and infection: etiologic agents, onset, duration, symptoms, and treatment.
4. How would you differentiate between salmonellosis and botulism?
5. Why do urinary tract infections frequently occur after catheterization procedures?
6. Why is botulism the most serious form of bacterial food poisoning?
7. Why is tuberculosis still a problem in underdeveloped countries? In the United States?
8. What is the standard treatment for most bacterial diarrheas?
9. Why are most cases of gastroenteritis not treated with antibiotics?
10. How are tetanus, gas gangrene, and botulism related?

Critical Thinking Questions

1. Why is tetanus a concern only when one has a deep puncture-type wound and not a surface cut or abrasion?
2. Think about our modern, Western lifestyles. Can you name and describe bacterial diseases that result from this life of relative luxury?
3. You have been assigned the task of eradicating gonorrhea in your community. Explain how you would accomplish this.
4. You are a park employee. How would you treat people from acquiring arthropod-borne diseases?
General


Chapter 39 Human Diseases Caused by Bacteria


39.4 Food-Borne and Waterborne Diseases


39.5 Sepsis and Septic Shock


39.6 Dental Infections


