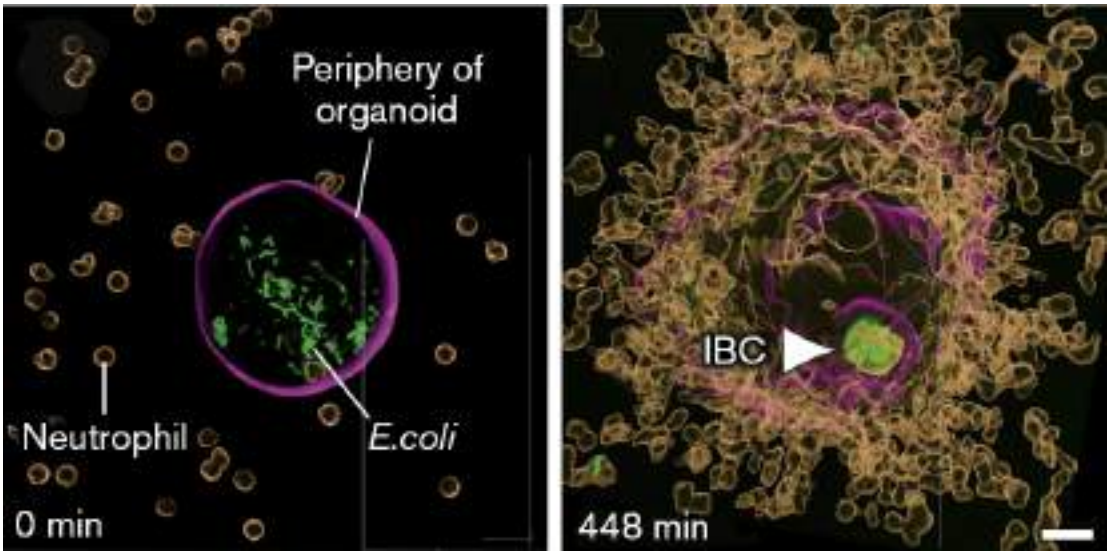
CHAPTER 26

Microbial Diseases



Urinary tract infections (UTIs) in miniature. Why do people, especially women, develop recurrent UTIs? Panels show a tiny (250-µm diameter), bladder organoid used to study UTIs. *Escherichia coli* (green) injected into the organoid grow in the luminal space, but a few bacteria enter bladder cells to form intracellular bacterial colonies (IBCs) protected from antibiotics and neutrophils (panel 1). Neutrophils added outside an infected organoid will swarm into the organoid and kill lumen bacteria, but they cannot kill the IBC bacteria (panel 2, arrowhead). IBC bacteria can emerge later to reinfect the lumen. Scale bar = 20 µm.

K. SHARMA ET AL. 2021. *CELL REP* . **36**

Chapter Sections		Learning Objectives
26.1 Basics of Diagnosis and Infections of Skin, Soft Tissue, and Bone	»	Illustrate how patient histories are used to develop diagnostic differentials, and how variations in symptoms or disease severity among patients can complicate diagnosis.
	»	Define the key features of skin, soft tissue, and bone infections.
26.2 Respiratory Tract Infections	»	Explain and differentiate among respiratory tract infections such as bacterial pneumonia, tuberculosis, fungal pneumonia, and viral pneumonia.
26.3 Gastrointestinal Tract Infections	»	Develop differentials for various bacterial, viral, and protozoan diseases of the gastrointestinal tract, including ulcers, diarrhea, and liver disease.

Chapter Sections		Learning Objectives
26.4 Genitourinary Tract Infections	»	Present key clinical and pathogenic features of urinary tract infections and sexually transmitted infections.
26.5 Cardiovascular and Systemic Infections	»	Discuss the pathogenesis, symptoms, and treatments for sepsis, systemic infections, and cardiac infections.
Special Topic 26 How Neutrophils Ambush *Staphylococcus aureus* in a Lymph Node		
26.6 Central Nervous System Infections	»	Use symptoms, diagnostics, and elements of pathogenesis to distinguish among infections of the central nervous system.
eResearch Activity 26 Can a Microbiome "Learn" from an Infection?		

Infectious diseases have challenged human existence for millions of years. Even today, with our diagnostic acumen and myriad

treatment choices, the impact of infectious disease on the world's population is staggering. The number of infection-related deaths of immunocompetent individuals, combined with the number of people who are immunocompromised by conditions such as cancer, smoking, or drug abuse, makes infectious disease the leading contributor to death in the world.

Over 1,400 different pathogenic species of viruses, bacteria, fungi, and protozoa are known to infect humans. The latest major assault came from the novel coronavirus SARS-CoV-2, the cause of COVID-19, a disease that nearly brought humanity to its knees and tested our resolve beyond recent memory. Our tenacity as a species is due in large part not only to our immune system but also to our capacity to diagnose, treat, and prevent known infections as well as spot newly emerging ones.

In this chapter we introduce the art of diagnosis and explore the major types and etiologies of infections. We discuss a wide variety of infectious microbes by describing their routes of infection, the pathologies they cause, and the symptoms that result. We do not present an exhaustive compendium of microbial illnesses but instead a representative sampling of them that illustrates key aspects of microbial disease. The diseases selected, including COVID-19, are presented as a clinician views them: by the organ system affected, not by the taxonomy of the pathogen. The advantage of our strategy is diagnostic. When examining a sick patient, a clinician must first determine which organ system is affected and then mentally sort through the pathogens known to affect that system. This approach will help you better integrate your knowledge of microbiology and immunology within the framework of the practice of medicine.

Because patient histories are so helpful in diagnosing infectious diseases, we also use case histories throughout this chapter to segue into discussions of the various microbes that can infect each organ system. Key aspects of infectious diseases will emerge.

26.1 Basics of Diagnosis and Infections of Skin, Soft Tissue, and Bone

How is a diagnosis made? It is not a simple matter of taking a specimen, ordering a test, and prescribing a drug. The clinician first needs to figure out which microbes, out of thousands, are possible causes. When you go to the clinic, what does a clinician first ask? "What brings you here today?" followed by "How long have you had these symptoms?" and perhaps "Where have you traveled recently?" This is not idle conversation; the clinician is collecting data by taking a patient history (**Fig. 26.1**).



FIGURE 26.1 ■ Clinician taking a patient history.
ROCKETCLIPS, INC./SHUTTERSTOCK

Because many infectious diseases display similar symptoms, a patient history can provide clues about the likely culprit. For example, *Vibrio cholerae* and enterotoxigenic *E. coli* both produce diarrheal diseases characterized by cramps, lethargy, and liters of watery stool each day, but cholera is not commonly seen in the United States. Nevertheless, a clinician might suspect cholera if the patient recently traveled to, or emigrated from, a part of the world where cholera is endemic (regularly observed). Clinicians learn this information by talking with the patient and asking about their recent travels.

Note: We recognize that gender identity is an important issue. Not everyone identifies as strictly male or female. However, the spectrum of recognized gender identities can make discussions of medical issues difficult. To simplify our explanations of infectious disease, we use the terms "male" and "female" solely to indicate reproductive anatomy, not gender.

Many questions the clinician asks while taking a patient's social history can seem irrelevant or even intrusive to the patient, who only wants relief from the symptoms. For instance: Do you have any hobbies? What is your occupation? What foods have you eaten recently? Does your ill child attend day care? Has anyone in your family had similar symptoms? All of those questions address possible sources of the infectious agent. Other questions can reveal high-risk behavior that can lead to certain infections. Do you smoke, drink, or take recreational drugs? Have you had multiple sex partners? Do you use contraception? If a woman seeking help for abdominal pain reveals that she has multiple sex partners who don't use condoms, then the differential , the list of possible causes of her symptoms, should include gonorrhea, syphilis, and chlamydia. A good patient history combined with a thorough physical exam helps the clinician decide which further tests to order and which procedures to perform.

However, different people infected with the same pathogen can display somewhat different symptoms. This variation can sometimes complicate diagnosis. For instance, some patients infected with measles virus develop muscle pain, whereas other patients do not. A small number of patients infected with measles virus develop life-threatening encephalitis, but most do not. Why do disease symptoms and severity differ among patients? Part of the explanation is immunocompetence. Those with more effective immune systems can better defend themselves against the pathogen. As a result, some infected people may not develop any symptoms. However, genetic differences in immunocompetence are only part of the story.

Uri Sela (Rockefeller University) and colleagues discovered that pangenomic gene differences between different strains of a pathogen will also alter a patient's immune response (the concept of pangenome versus core genome was introduced in Chapter 17). In one experiment the scientists examined 16 different heat-killed *Staphylococcus aureus* strains (clinical isolates) for their abilities to stimulate T-cell proliferation and interferon-gamma (IFN-gamma) production in vitro using lymphocytes from a single volunteer (**Fig. 26.2**). T-cell proliferation and IFN-gamma production are markers of the immune response to infection (see Chapter 24). Even though

the bacteria were dead, the different strains stimulated different levels of T-cell proliferation and IFN-gamma production. That is, a single host displayed a heterogeneous response to the different strains of *S. aureus* . This finding and other data indicate that the final immune response of a host is due as much to pathogen strain variability as it is to individual host variability. Both of these parameters can complicate diagnosis, treatment, and patient outcome.

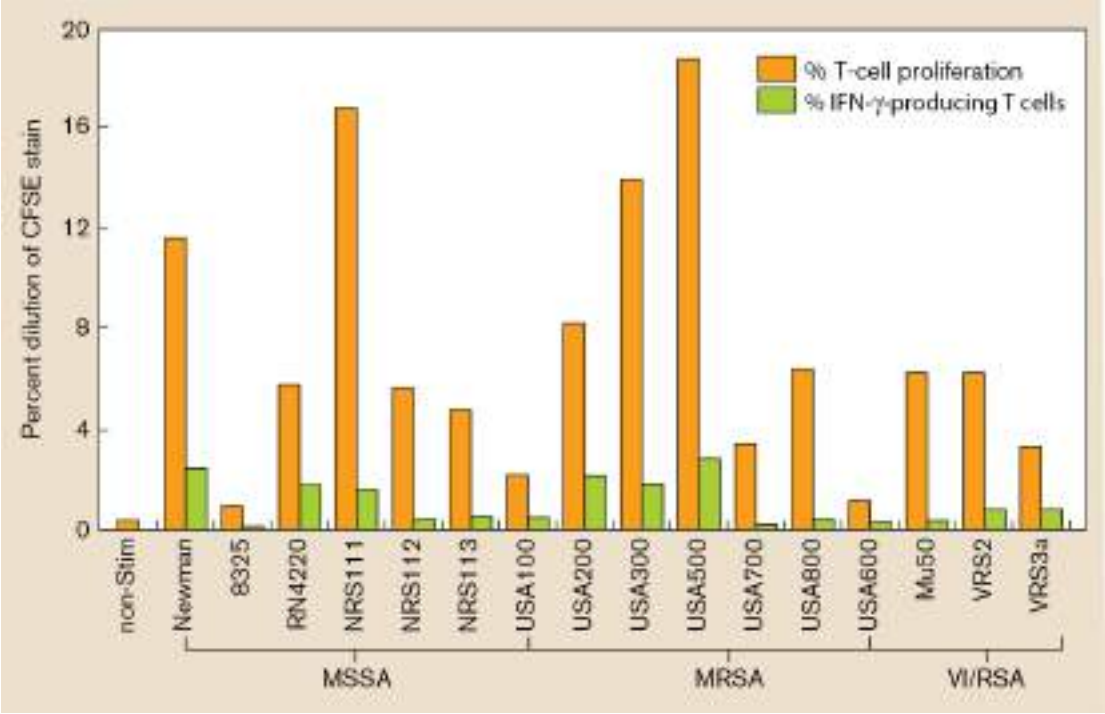


FIGURE 26.2 ■ The immune response of a host varies with pangenomic differences in *Staphylococcus aureus* strains. Lymphocytes from a single host were tested in vitro for the ability to respond to 16 different heat-killed strains of *S. aureus* (designated by number or name along the *x* -axis). MSSA = methicillin-sensitive *S. aureus* ; MRSA = methicillin-resistant *S. aureus* ; VRSA = vancomycin-resistant *S. aureus* . T-cell proliferation was determined by staining T cells with CFSE (carboxyfluorescein succinimidyl ester) stain and monitoring dilution of the stain per cell as the cells proliferated. Every time a cell containing stain replicated, the stain was divided (diluted) into the two new cells. T cells that produced IFN-gamma were identified by fluorescent antibody followed by FACS analysis. non-Stim = T cells not stimulated by heat-killed *S. aureus* .

Source: Modified from Sela et al. 2018. *PLoS Pathog* . **14** :e1006726, fig. 1A.

Infections of Skin, Soft Tissue, and Bone

Bones, skin, and soft tissues such as muscle and underlying connective tissues collectively shape and maintain body architecture. Because these structures are interconnected, infections that threaten the integrity of bones, skin, and soft tissues are discussed together. Infections that affect one of these tissues can also spread directly to an adjacent tissue.

Skin and soft-tissue infections range from simple boils to severe, complicated, so-called flesh-eating diseases that can be caused by a variety of bacteria, fungi, and viruses (see Table 26.1). Recall that the integrity of the skin, as well as the presence of normal skin microbiota, prevents most infections. However, even minor insults to the skin (such as a paper cut) can result in infections, most of which are caused by the Gram-positive pathogen *Staphylococcus aureus* . Healthy individuals develop infections of the skin only rarely, whereas people with underlying immunosuppressive diseases, such as diabetes, are at much higher risk.

TABLE 26.1 Common Infectious Diseases of the Skin

Disease	Symptoms	Etiological agent(s) [a]	Virulence factors
Bacterial			
Folliculitis	Boils	*Staphylococcus aureus* (G+ cocci); fibrin wall around abscess renders it poorly accessible to antibiotics	Coagulase, protein A, TSST, leukocidin, exfoliative toxin
Scalded skin syndrome	Peeling skin on infants, systemic	*S. aureus* (G+ cocci)	Disseminated exfoliation

TABLE 26.1	Common Infectious Diseases of the Skin		
	toxin		exotoxin
Impetigo	Skin lesions on the face, mostly in children	*S. aureus* or *Streptococcus pyogenes* (G+ cocci)	Various, as for boils
Scarlet fever	Sore throat, fever, rash	*S. pyogenes* (G+ cocci)	M-protein pili, C5a peptidase, hemolysin, pyrogenic toxins, others
Erysipelas	Skin lesions, usually facial, that spread to cause systemic infection	*S. pyogenes* (G+ cocci)	As for scarlet fever (see above)
Cellulitis	Uncomplicated infection of the dermis	*S. aureus* , *S. pyogenes*	As for scarlet fever (see above)
Necrotizing fasciitis	Rapidly progressive cellulitis	*S. aureus* , *S. pyogenes* , *Clostridium perfringens (* G+ spore-forming rod anaerobe *)*	As for scarlet fever (see above); a variety of toxins

TABLE 26.1	Common Infectious Diseases of the Skin		
		Vibrio vulnificus (G − rod)	
Viral			
Rubella [b]	Discolored, pimply rash; mild disease unless congenital	Rubella virus [ssRNA(+)]	Envelope proteins E1 and E2
Measles [b]	Severe disease, fever, conjunctivitis, cough, rash	Rubeola virus [ssRNA(−)]	V protein (interferes with interferon signaling)
Chickenpox [b]	Generalized discolored lesions	Varicella-zoster (dsDNA)	Glycoprotein B (fusion of viral and cell membranes)
Shingles [b]	Pain and skin lesions, usually on trunk in adults	Varicella-zoster (dsDNA)	Glycoprotein E (required for cell-cell fusion)
Smallpox [c]	Raised, crusted skin rash, highly contagious	Variola major (dsDNA)	SPICE (smallpox inhibitor of

TABLE 26.1	Common Infectious Diseases of the Skin		
			complement enzymes)
Warts [b]	Rapid growth of skin cells	Papillomaviruses (dsDNA)	E6 and E7 oncoproteins (see Section 26.5)
Fungal			
Dermatophytosis	Dry, scaly lesions like athlete's foot (tinea pedis)	Dermatophytes (*Epidermophyton, Tricophyton, Microsporum*)	Unclear
Sporotrichosis	Granulomatous, pus-filled lesions; can disseminate to lungs or other organs	*Sporothrix schenckii*	Melanin
Blastomycosis	Granulomatous, pus-filled lesions; can disseminate to lungs or other organs	*Blastomyces dermatitidis*	BAD1 adherence
Candidiasis	Patchy inflammation of mouth (thrush) or vagina; can	*Candida albicans;*	Proteinase, phospholipase, Ssn6/Tup1

TABLE 26.1	Common Infectious Diseases of the Skin		
	disseminate in immunocompromised patients	*Candida glabrata*	regulators, others
Aspergillosis	Infected wounds, burns, cornea, external ear	*Aspergillus spp.*	PacC/FOS1 regulators, gliotoxin
Zygomycosis	Oropharyngeal infections; affects mainly diabetic patients; can rapidly disseminate	*Mucor and Rhizopus spp.*	Iron acquisition (rhizoferrin); rhizoxin

Boils

Staphylococcus aureus (**Fig. 26.3A**) is a common cause of painful skin infections called boils or furuncles. This Gram-positive organism, often a normal inhabitant of the nares (nostrils), can infect a cut or gain access to the dermis via a hair follicle. It possesses a number of enzymes that contribute to disease, including coagulase, which helps coat the organism with fibrin, thereby walling off the infection from the immune system and antibiotics. As a result, boils generally require surgical drainage in addition to antibiotic therapy.



FIGURE 26.3 ■ *Staphylococcus aureus* . A. *S. aureus* (colorized SEM). **B.** Exfoliative toxin from some strains of *S. aureus* causes scalded skin syndrome.

DENNIS KUNKEL MICROSCOPY/SCIENCE SOURCE
DR. KEN GREER/VISUALS UNLIMITED, INC.

As noted in Chapters 24 and 25 , some strains of *S. aureus* also produce toxic shock syndrome toxin (TSST), a superantigen that can lead to serious systemic symptoms. Recall that a superantigen links and activates antigen-presenting cells and T cells by binding to the outside of MHC class II receptors and T-cell receptors. Antigen recognition is not required. As a result, many different T cells become activated to release a flood (or storm) of cytokines.

A particularly dangerous strain of *S. aureus* is called methicillin-resistant *S. aureus* (MRSA). Today, infections suspected to be caused by *S. aureus* are treated with penicillin-like drugs, such as oxacillin (similar to methicillin). MRSA strains, however, have developed resistance to methicillin, oxacillin, and many other penicillin-like drugs through an altered penicillin-binding protein (PBP) involved in cell wall synthesis (see the discussion of MecA in Section 27.2). So, using oxacillin or amoxicillin to treat what turns out to be a MRSA infection will result in treatment failure that can become life-threatening. Once the mistake is discovered, immediate use of alternative drugs, such as vancomycin, is required.

MRSA strains, originally discovered causing hospital-acquired (nosocomial) infections, are now commonly found outside hospitals. MRSA and other infections can develop during a visit to any health care facility, such as hospitals, nursing homes, doctor offices, or rehabilitation facilities. These infections are now referred to as health care–associated infections (HAIs) . Another category, called community-acquired infections (CAIs), especially MRSA, can develop in individuals who have not recently encountered health

care. HAI-MRSA and CAI-MRSA infections are occurring at an epidemic rate in the United States (an incidence of approximately 20 per 100,000 population).

Seventy percent of staphylococcal skin infections are now caused by MRSA, and 30% of the U.S. population have their skin or nostrils colonized by MRSA. Thus, a physician can no longer assume that a patient walking into the office with a staphylococcal infection will respond to methicillin-like drugs such as oxacillin. The doctor must assume that the infection may be caused by MRSA. As a result, treatment regimens around the country and the world are being forced to change. Today, vancomycin and linezolid are initially used to treat serious infections where MRSA is a suspected cause (treatments will vary depending on antibiotic resistance patterns in the community). Once the clinical laboratory rules out MRSA, the antibiotic treatment is changed. Antibiotics are discussed in Chapter 27 .

Other staphylococcal diseases are caused by toxin-producing strains in which the organism remains localized but the toxin disseminates. We have already mentioned TSST, but there are other toxins. For example, some strains of *S. aureus* produce a toxin called exfoliative toxin, which causes a blistering disease in children called staphylococcal scalded skin syndrome (**Fig. 26.3B**). Like TSST, exfoliative toxin is a superantigen (described in Section 24.3). In addition, exfoliative toxin cleaves a skin cell adhesion molecule that, when severed, results in the epithelium separating from the underlying dermis (blisters).

Thought Question

26.1 Does *Staphylococcus aureus* have to disseminate through the circulation to produce the symptoms of scalded skin syndrome (SSS)? Explain why or why not.

Case History: Necrotizing Fasciitis by "Flesh-Eating" Bacteria

One weekend in June, Cassi was camping with her three children. She suffered a minor cut on her finger, which she bandaged properly. She also injured the left side of her body while playing sports with her kids. Not thinking much of either of her minor injuries, she went to bed. Two days later, Cassi was extremely ill. Her symptoms included vomiting, diarrhea, and a fever. She was

also in severe pain where she had injured her side, and the area had begun to bruise (the skin was not broken). By the next day she could barely get out of bed, and by the end of that night she was having difficulty breathing and could not see. Within hours her side worsened and began to leak fluid and blood. Cassi was admitted to the hospital in septic shock, with no detectable blood pressure. An infectious disease specialist looking at the wound (similar to ***Fig. 26.4A*** *) diagnosed the problem as necrotizing fasciitis. Cassi also developed sepsis, which led to dangerously low blood pressure. Because necrotizing fasciitis is often deadly, Cassi was rushed into surgery. In an effort to save her life, the surgeons removed about 7% of her body surface. The large wound infection in her side would need to resolve before a skin graft could be performed to repair it, so the hole in Cassi's body was left wide open for days. After nearly 3 months and several operations, Cassi recovered.*

What kind of organism can cause this type of devastating disease? The disease necrotizing fasciitis , also known incorrectly as "flesh-eating disease," is rare and is often caused by the Gram-positive coccus *Streptococcus pyogenes* (**Fig. 26.4B**), a microbe normally associated with throat infections (pharyngitis). Although sometimes described as a recently emerging infectious disease, necrotizing fasciitis was first discovered in 1783, in France.

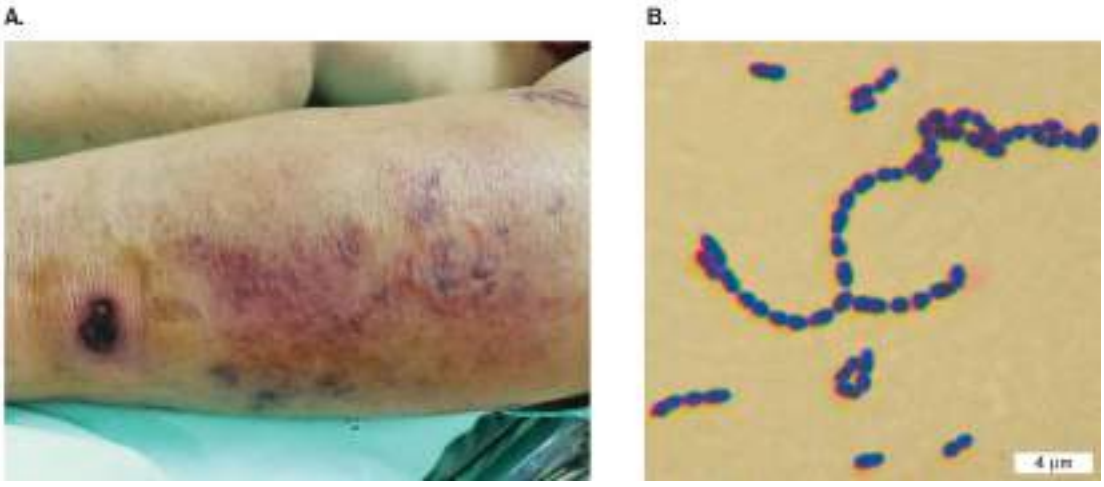


FIGURE 26.4 ■ Flesh-eating *Streptococcus pyogenes* . A. Early-stage wound of necrotizing fasciitis. **B.** Gram stain of *S. pyogenes* . Each cell is approx. 1 µm in diameter.

ANDA PHOTO/SHUTTER STOCK
COURTESY OF DR. WILLIAM SCHWAN

In this case history, Cassi probably had this organism on her skin when the injury to her side occurred. The injured area probably suffered an invisible

microabrasion, providing a good growth environment for the organism, leading to the secretion of potent toxins and death of surrounding tissues. The bacteria will spread through subcutaneous tissue, destroying fat and fascia without initially harming the skin itself. Fascia is the sheath of thin, fibrous tissue that covers muscles and organs.

Rapid, aggressive surgical removal of affected tissue and immediate treatment with antibiotics are required in these extreme cases, even before the clinical microbiology lab has had time to identify the organism. In this approach to antibiotic treatment, called empiric therapy , one or more antibiotics are given to "cover" (kill) the most likely causative agents. Therapy can include clindamycin and metronidazole (both of which act against anaerobes and Gram-positive cocci) and gentamicin or piperacillin (drugs particularly effective against Gram-negative microbes). (Chapter 27 further discusses these and other antibiotics.) Often, however, antibiotic treatment of patients with necrotizing fasciitis is difficult because of insufficient blood supply to affected dead tissues.

Other bacteria can also cause necrotizing fasciitis, such as *Staphylococcus aureus* and the marine organism *Vibrio vulnificus* . In rare cases (the most recent was documented in 2018), *Capnocytophaga canimorsus* , a Gram-negative bacterium unique to the mouths of dogs and cats, has caused necrotizing fasciitis in people who have been licked or bitten by a dog. *C. canimorsus* infections are very rare, however, because those most at risk are immunocompromised in some way.

Cellulitis is another form of skin infection but is less aggressive than necrotizing fasciitis. Cellulitis does not involve the fascia or muscles but is characterized by localized pain, swelling, tenderness, erythema, and warmth. *Streptococcus pyogenes* is the most frequent cause of cellulitis in immunocompetent adults but a number of other bacteria, including *Staphylococcus aureus* , Gram-negative bacilli, and anaerobes, can also cause this skin infection. Cellulitis can progress to necrotizing fasciitis if left untreated.

Streptococcus pyogenes wields many different virulence factors, such as the M protein used for nonpilus attachment and inflammasome activation, various superantigen exotoxins, and secreted enzymes such as hyaluronidase and DNase (some of these are described in Chapter 25). Many established virulence factor genes in *S. pyogenes* are located on prophages (phage genomes) integrated into the bacterial genome. Prophages constitute approximately 10% of the organism's genome. One study found that a soluble factor produced by human pharyngeal cells could facilitate activation of at least some of these phages and cause horizontal transfer of the associated virulence

factors between strains of this pathogen. Prophage activation and phage production are discussed in Chapter 6 .

Thought Question

26.2 Why would treatment of some infections require multiple antibiotics?

Osteomyelitis

Osteomyelitis is a bone infection with accompanying inflammation and bone destruction caused by bacteria. All bones can be infected, but the lower extremities and vertebrae are most commonly involved. Bone can be infected in several ways. Acute trauma or surgery can directly introduce organisms into affected bone, or organisms from an adjacent soft-tissue infection can spread to nearby bone. Organisms can also spread through the bloodstream from peripheral sites of infection (an abscess, for instance) to bone (called hematogenous seeding). Hematogenous seeding most commonly affects vertebrae because they are well vascularized.

The most common causes of osteomyelitis include staphylococci (*Staphylococcus aureus*), streptococci (*Streptococcus pyogenes*), Gram-negative bacilli (*Pseudomonas* , *Escherichia*), and some anaerobes (*Bacteroides*). Bone biopsy is usually needed to identify the organism. Host factors that contribute to osteomyelitis include diabetes (for instance, when a diabetic foot wound goes untreated), sickle-cell disease in children, joint prosthetics, and intravenous drug use. Antibiotic treatment of osteomyelitis is challenging because most bones are not well vascularized, so debridement (removal of damaged tissue) is also necessary.

Viral Diseases Causing Skin Rashes

Several viruses can produce skin rashes, although their route of infection is usually through the respiratory tract. Measles, for example (see Section 6.1), is a highly contagious viral infection caused by a paramyxovirus, whose hallmark symptom is a maculopapular skin rash (see Fig. 6.3D). In a maculopapular rash, flat, red (macular) spots are intermixed with raised bumps (papules). The virus is transmitted by coughing and sneezing, but the first

signs of measles, also known as rubeola, are fever, cough, runny nose, and red eyes occurring 9–12 days after exposure. A few days later, telltale spots (Koplik's spots) appear in the mouth, along with a sore throat. Then a skin rash develops that typically starts on the face and spreads down the body. The virus replicates in the lymph nodes and spreads to the bloodstream (viremia), where it can infect endothelial cells of the blood vessels. The rash occurs when T cells begin to interact with these infected cells.

Although skin rash is the main symptom of measles, infection can also cause respiratory symptoms and serious complications, including pneumonia, bronchitis, croup, and even a fatal encephalitis in immunocompromised patients. Approximately one out of four cases of measles requires hospitalization. One out of 1,000 dies. In the United States, measles had been almost completely eliminated by the measles, mumps, and rubella (MMR) multivalent vaccine. Unfortunately, a disturbing, misinformed anti-vaccine movement over the past two decades has led to a decrease in vaccinations and an increase in U.S. measles cases. Case numbers in the United States for 1999 were 100 and by 2019 had risen to 1,282. In 2020, measles cases dropped dramatically to 13, as public health measures implemented for the COVID-19 pandemic curtailed the transmission of measles and many other airborne infectious diseases. As these restrictions are relaxed, however, experts expect cases of measles and other preventable infections will once again rise. Worldwide, however, measles has remained a serious problem, killing 207,000 people in 2020, including in places where vaccinations are routine.

Rubella virus, a togavirus, causes a maculopapular rash known as German measles or 3-day measles. The rash is similar to but less red than that of measles (**Fig. 26.5**). German measles is an infection of primarily the skin and lymph nodes and is usually transmitted from person to person by aerosolization of respiratory secretions. It is not dangerous in adults or children; the virus can, however, cross the placenta in a pregnant woman and infect her fetus. If the virus crosses the placenta within the first trimester, the result is congenital rubella syndrome, which can cause death or serious congenital defects in the developing fetus.

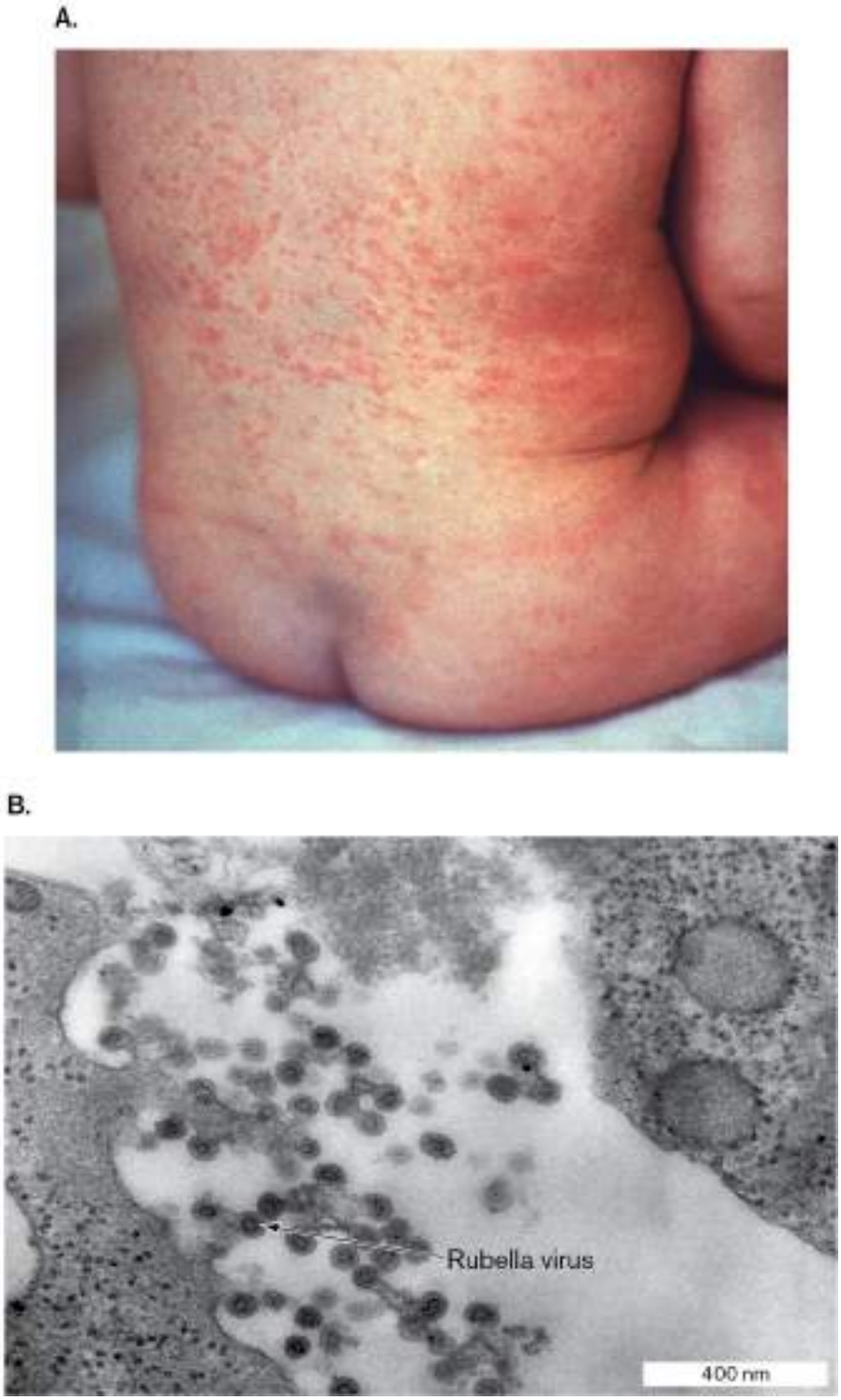


FIGURE 26.5 ■ German measles. A. Skin rash caused by rubella virus. **B.** Rubella virus budding from the host cell membrane to form an enveloped virus particle (approx. 50–70 nm; TEM).

CENTERS FOR DISEASE CONTROL AND PREVENTION/SCIENCE SOURCE
CDC/DR. FRED MURPHY; SYLVIA WHITFIELD

Human papillomavirus (HPV) is a common virus (over 100 types) that causes warts, abnormal skin growths on feet, hands, or genital organs (**Fig. 26.6**). The replication of HPV is discussed in Section 6.5 . The virus enters the skin through small cuts or abrasions and then replicates in the basal epithelial cells. The virus causes excessive growth of the cells it infects, in part by triggering overexpression of host c-Myc protein, which is needed for mitosis. Excess c-Myc (an oncoprotein) causes uncontrolled cell division that produces warts or, in the worst-case scenario, cervical or penile cancer. After the initial infection has resolved, the virus may remain latent in tissues and can reactivate if immune system function is impaired. Cryosurgery with liquid nitrogen to freeze the growth will remove most common warts. Genital HPV is more dangerous than common warts, and it is a common sexually transmitted infection among college students.



FIGURE 26.6 ■ Noncancerous hand warts caused by human papillomavirus (HPV).

CLINICAL PHOTOGRAPHY, CENTRAL MANCHESTER UNIVERSITY HOSPITALS NHS FOUNDATION TRUST, UK/SCIENCE SOURCE

Infection by any of several different types of HPV can produce cervical and penile cancers years after infection (see Fig. 6.31A). As with common warts, cryosurgery can be used to treat genital HPV growths, but preventing the

disease is more effective and less painful. Prevention is provided by Gardasil, a 9-valent vaccine that prevents infection by the most common cancer-causing types: HPV16, HPV18, and seven others. The U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) recommend administering the vaccine to young people between ages 9 and 26, ideally before they become sexually active and potentially encounter the virus. Unfortunately, most kids in the United States do not receive it.

Other viruses affecting the skin, such as chickenpox, the related disease shingles, and smallpox are included in Table 26.1 . The vaccination schedule for preventing these diseases is provided in Table 24.5 .

To Summarize

- ***Staphylococcus aureus* and *Streptococcus pyogenes*** are common bacterial causes of skin infections. The organisms usually infect through broken skin.
- **Methicillin-resistant *Staphylococcus aureus* (MRSA)** has become an important cause of community-acquired staphylococcal infections (CAI-MRSA).
- **Necrotizing fasciitis** is usually caused by *Streptococcus pyogenes* , but it can be the result of other infections.
- **Infections of the skin** can disseminate via the bloodstream to other sites in the body.
- **Osteomyelitis** , usually caused by *Staphylococcus aureus* , begins with direct bone trauma, hematogenous seeding, or contact with a nearby soft-tissue infection.
- **Rubeola and rubella viruses** (RNA viruses) infect through the respiratory tract, but their main manifestation is the production of similar maculopapular skin rashes.
- **Human papillomaviruses** (DNA viruses) enter through skin to cause warts on skin; some types can cause genital cancers.

Glossary

differential
: In disease, the list of possible causes of an infection.

nosocomial

Hospital-acquired; commonly refers to an infectious agent.

health care–associated infection (HAI)

Any infection contracted by a patient while receiving treatment for a medical condition at a health care facility, such as hospitals, nursing homes, doctor offices, or rehabilitation centers.

necrotizing fasciitis

Also known as *flesh-eating disease* . A severe skin infection usually caused by the Gram-positive coccus *Streptococcus pyogenes* .

empiric therapy

An approach to treating infection before the infective organism is known, in which multiple antibiotics are administered in an effort to kill the most likely causative agents.

cellulitis

A spreading infection (with inflammation) of connective tissue just below the skin.

Fig. 6.3D

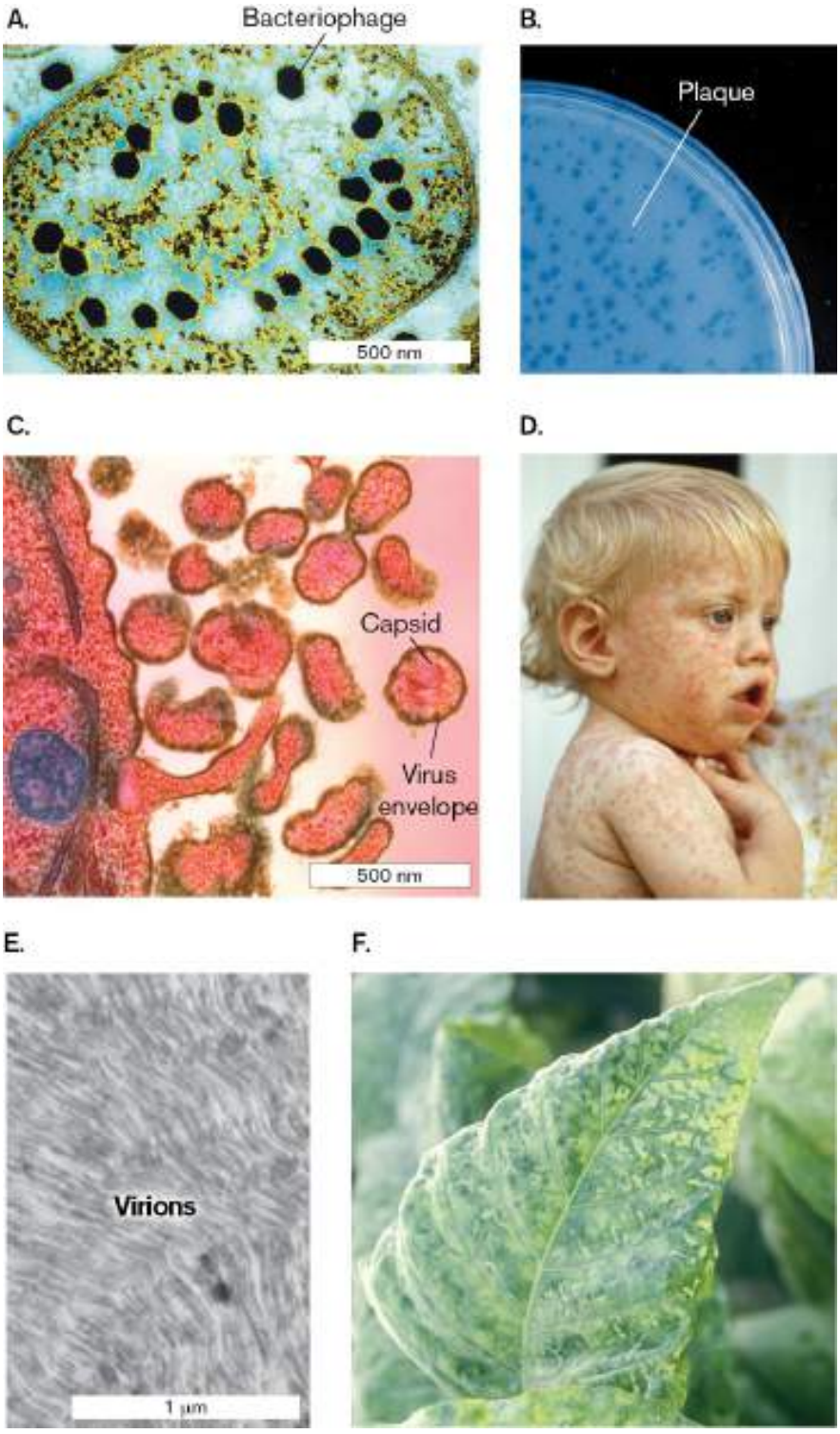


FIGURE 6.3 ■ Virus infections and disease. A. Bacteriophage T2 particles pack in an array within an *Escherichia coli* cell (TEM). **B.** Bacteriophage infection forms plaques of lysed cells on a lawn of bacteria. **C.** Measles virions bud out of human cells in tissue culture

(TEM). **D.** Child infected with measles shows a rash of red spots. **E.** Tobacco leaf section is packed with tobacco mosaic virus (TMV) particles. **F.** Tomato leaf infected by TMV shows mottled appearance.

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NORM THOMAS/SCIENCE SOURCE

Fig. 6.31A

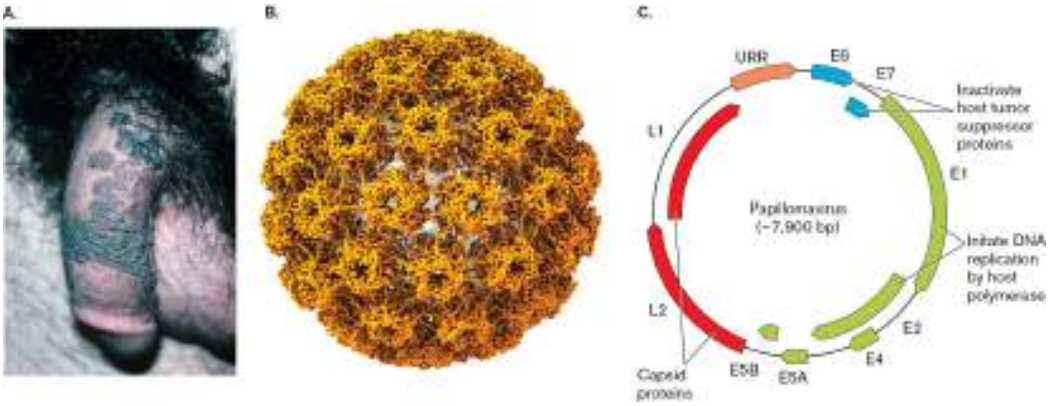


FIGURE 6.31 ■ Human papillomavirus. A. Certain strains of human papillomavirus (HPV) cause warts on the genitals or anus. **B.** HPV virion model (cryo-EM). **C.** HPV genome.

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Endnotes

1. Note a: G+ = Gram-positive. Return to reference a
2. Note b: Vaccine is available against the causative agent. Return to reference b
3. Note b: Vaccine is available against the causative agent. Return to reference b
4. Note b: Vaccine is available against the causative agent. Return to reference b
5. Note b: Vaccine is available against the causative agent. Return to reference b
6. Note b: Vaccine is available against the causative agent. Return to reference b

7. Note c: Vaccine is no longer in use because the disease has been eradicated. The exceptions are highly restricted laboratories. Return to reference c

26.2 Respiratory Tract Infections

Lung and upper respiratory tract infections are among the most common diseases of humans. Many different bacteria, viruses, and fungi are well adapted to grow in the lung. Successful lung pathogens come equipped with appropriate attachment mechanisms and countermeasures to avoid various lung defenses (such as alveolar macrophages). One reemerging bacterial pathogen, *Bordetella pertussis* , the cause of whooping cough, inhibits the mucociliary escalator by binding to lung cilia (**Fig. 26.7**). Although many microbes can infect the lung, most respiratory diseases are of viral origin, and most viral respiratory infections (such as the common cold) do not spread beyond the lung. Viral diseases are usually self-limiting and typically resolve within 2 weeks; however, the damage caused by a primary viral infection can lead to secondary infections by bacteria. Other viral diseases, such as influenza and COVID-19, can be deadly in their own right.

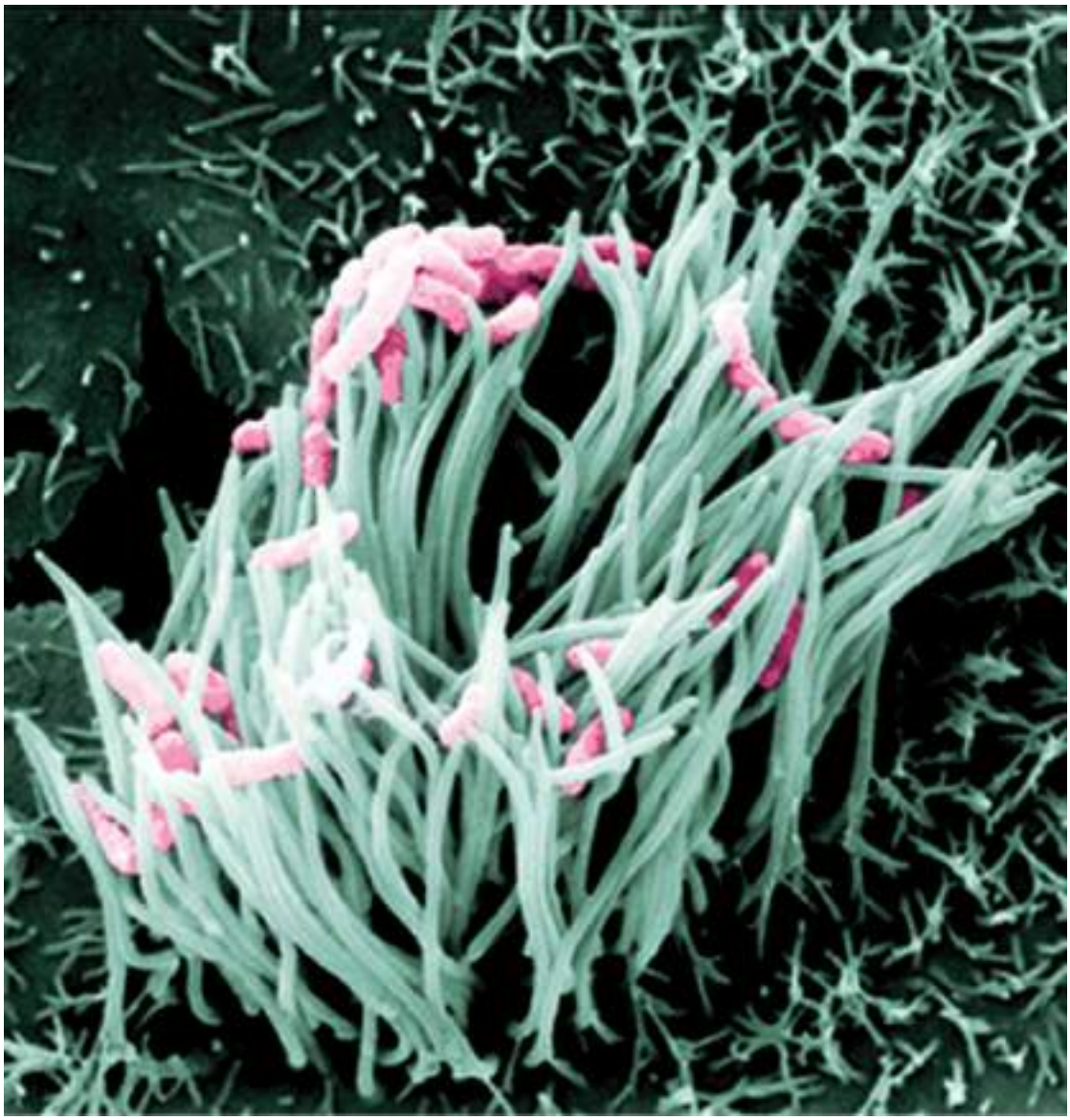


FIGURE 26.7 ■ Rabbit tracheal epithelial cells infected with *Bordetella bronchiseptica* . Primary cultured rabbit tracheal epithelial cells, following 5 minutes of

coincubation with virulent wild-type *B. bronchiseptica* . *B. bronchiseptica* is a close relative of *B. pertussis,* the cause of human pertussis (whooping cough). Bacteria (approx. 1 μm in length) have been pseudocolored pink for easier visualization (SEM).

JESSICA A. EDWARDS, ET AL. INFECTION AND IMMUNITY 2005. 73(6):3618–3626.

Bacterial infections of the lung, whether of primary or secondary etiology, require antibiotic therapy. Before the advent of antibiotics, the only recourse was to insert a tube into the patient's back to drain fluid accumulating in the pleural cavity around the lung (a pathological process known as pleural effusion). Unless released, the pressure on the lung will collapse the alveoli and make breathing difficult.

Viral infections predispose patients to secondary bacterial infections in several ways. Viral lung infections cause the patient to dehydrate, which increases mucus viscosity in the airways. Increased mucus viscosity limits motility of the mucociliary escalator (described in Section 23.1), making it harder to eliminate bacterial pathogens. To keep the escalator moving, cold sufferers are advised to drink plenty of fluids to decrease mucus viscosity. Another factor leading to secondary bacterial infections is that viruses can inhibit key aspects of lung innate immune mechanisms that prevent bacterial growth. Note that many deaths resulting from viral influenza are caused by secondary bacterial infections.

Case History: Bacterial Pneumonia

*James, an 80-year-old resident of a New Jersey nursing home, had a fever accompanied by a productive cough with brown sputum (mucous secretions of the lung that can be coughed up). He reported to the attending physician that he had pain on the right side of his chest and suffered from night sweats. Blood tests revealed that his white blood cell (WBC) count was 14,000 per microliter (normal is 5,000–10,000), with a makeup of 77% segmented forms (polymorphonuclear leukocytes, PMNs; normal range 40%–60%) and 20% bands (immature PMNs; normal range 0%–5%). The chest radiograph revealed a right-upper-lobe infiltrate (**Fig. 26.8A**). From this information, the clinician diagnosed pneumonia. Microscopic examination of the patient's sputum (Gram stain and capsule stain) revealed Gram-positive cocci in pairs and short chains surrounded by a capsule (**Fig. 26.8B**). Bacteriological culture of the patient's sputum and blood yielded* Streptococcus pneumoniae.

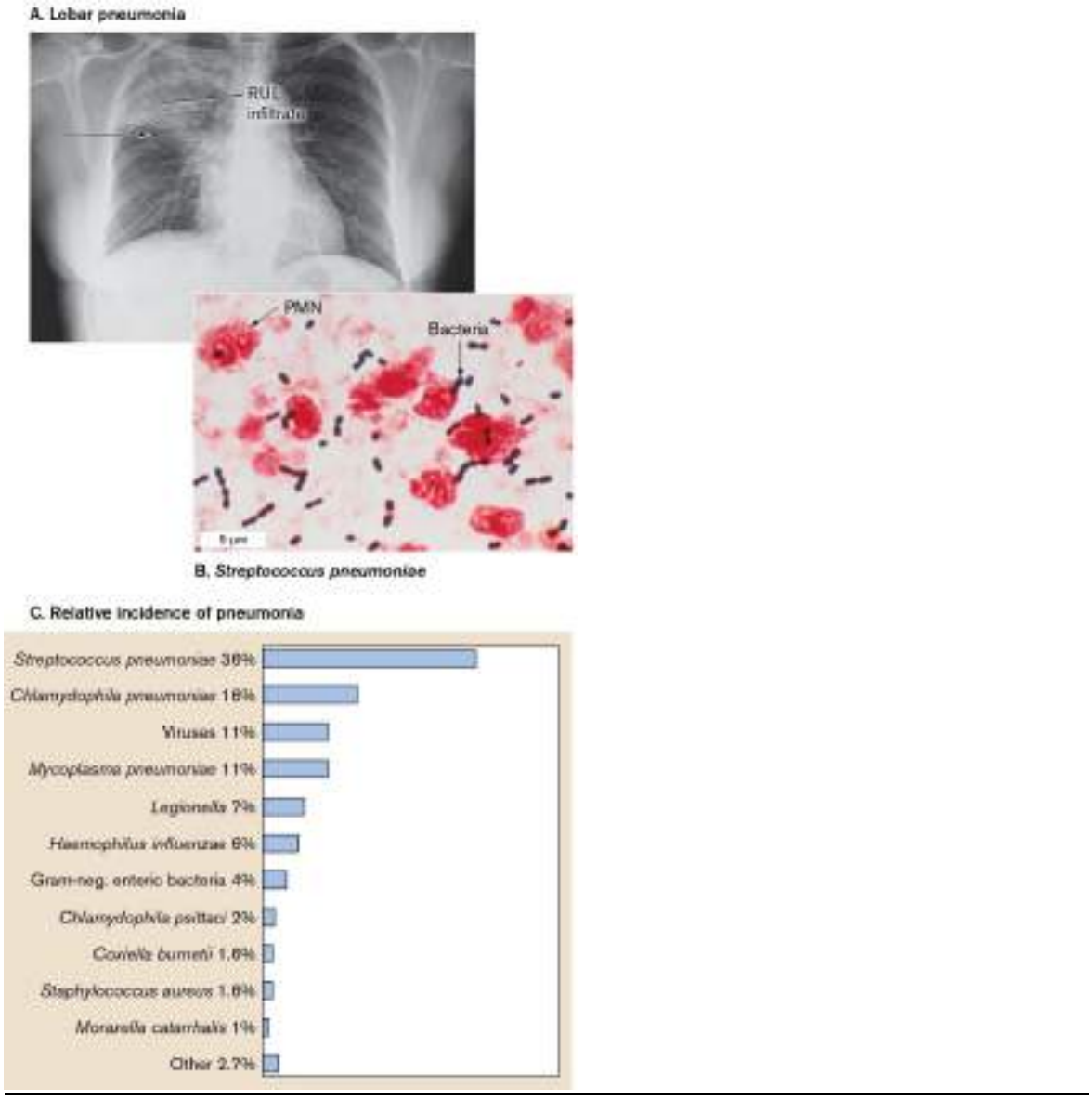


FIGURE 26.8 ■ Pneumonia caused by *Streptococcus pneumoniae.* A. X-ray view of a patient with lobar pneumonia. Infiltrate in the right upper lobe (RUL) is caused by *S. pneumoniae* . The sharp lower border of the infiltrate marks the upper boundary of the right middle lobe (arrow). **B** . Micrograph of *S. pneumoniae* . Gram-stained sputum sample showing numerous PMNs and extracellular diplococci in pairs and short chains. Bacteria range from 0.5 to 1.2 µm in diameter. **C.** Relative incidence of pneumonia caused by various microorganisms.

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Pneumonia is a disease that can be caused by many different microbes (Table 26.2). The pneumococcus *Streptococcus pneumoniae* accounts for about 25% of community-acquired cases of pneumonia (worldwide), but pneumococcal pneumonia occurs mostly among the elderly and immunocompromised, including smokers, diabetics, and alcoholics. A breakdown of pneumonia cases by causative organism is shown in **Figure 26.8C** .

TABLE 26.2	**Selected Respiratory Tract Infectious Diseases**			
Agent [disease]	**Key symptoms**	**Virulence properties**	**Source(s)**	**Treatment options (as of 2022)**
Bacterial				
Bacillus anthracis [anthrax]	Hypotension, respiratory failure	Peptide capsule; PA, LF, and EF toxins	Soil/airborne	Ciprofloxacin [vaccine (military)]
Corynebacterium diphtheriae [diphtheria]	Tracheal pseudomembrane	Diphtheria toxin	Humans	Penicillin (vaccine)
Streptococcus pneumoniae [pneumonia]	Fever, chills, cough, chest pain	Capsule, pneumolysin	Humans	Fluoroquinolones, ceftriaxone (vaccine)
Bordetella pertussis [whooping cough]	Violent cough, inhalation "whoop"	Adenylate cyclase toxin, filamentous hemagglutinin (adhesin)	Humans	Azithromycin (vaccine)
Pseudomonas aeruginosa [pneumonia]	Infects cystic fibrosis patients	Exotoxin A, phospholipase C, exopolysaccharide, others	Water, soil	Quinolones, aminoglycosides, carbapenems
Legionella pneumophila [Legionnaire's disease]	Chest pain, cough, muscle pain, vomiting	Intracellular growth, hemolysin, cytotoxin, protease	Water towers/ inhalation	Azithromycin (macrolide), quinolones
Chlamydia [a] *pneumonia* [pneumonia]	Sore throat, chest pain	Obligate intracellular growth; prevents	Humans	Tetracycline, macrolides

TABLE 26.2	Selected Respiratory Tract Infectious Diseases			
		phagolysosome fusion		
Chlamydia [a] *psittaci* [psittacosis]	Sore throat, chest pain	Obligate intracellular growth; prevents phagolysosome fusion	Bird droppings/ dust	Doxycycline, erythromycin
Mycobacterium tuberculosis [tuberculosis]	Cough, bloody sputum, fatigue, weight loss	Cord factor, wax D, intracellular growth	Humans	Rifampin, isoniazid, ethambutol, pyrazinamide [vaccine (BCG [b])]
Mycoplasma pneumoniae [pneumonia]	Sore throat, nonproductive cough	Adhesin tip	Humans	Azithromycin, doxycycline
Viral				
Cytomegalovirus (CMV) [CMV disease]	Cough, chest pain	Reduces MHC I presentation	Humans	Ganciclovir, valganciclovir
Respiratory syncytial virus (RSV) [RSV disease]	Cough, chest pain	Prevents T-cell activation	Humans	Treat symptoms/ribavirin, palivizumab [c]
Influenza virus [influenza]	Cough, chest pain	Neuraminidase; hemagglutinin	Humans	Zofluza, oseltamivir, zanamivir (vaccine)
Severe acute respiratory syndrome (SARS-CoV virus [SARS]	Cough, chest pain	Papain-like protease (PLP) inhibits type I interferon activities by	Humans	Treat symptoms/ dexamethasone, monoclonal Ab to spike protein,

TABLE 26.2	Selected Respiratory Tract Infectious Diseases			
and SARS-CoV-2 virus [COVID-19])		affecting host IRF-3; inhibits phosphorylation of, and cleaves, ubiquitin and ubiquitin-like ISG15 peptide from IRF-3		Paxlovid (protease inhibitor)
Fungal				
Aspergillus spp. [aspergillosis]	Lungs, sinuses; breathing difficulty	Dimorphism; gliotoxin	Environment	Amphotericin B, voriconazole
Histoplasma capsulatum [histoplasmosis]	Flu-like	Dimorphism; calcium-binding protein	Bird, chicken, bat droppings	Amphotericin B, itraconazole
Coccidioides immitis [coccidioidomycosis]	Flu-like	Dimorphism; arginase 1	Environment	Amphotericin B, fluconazole
Blastomyces dermatitidis [blastomycosis]	Flu-like	Dimorphism; BAD1	Environment	Amphotericin B, itraconazole
Pneumocystis jirovecii [pneumocystosis]	Chest pain, cough, skin lesion	Unknown	Environment	Bactrim

The noses and throats of 30%–70% of a given population can contain *S. pneumoniae* . The microbe can be spread from person to person by sneezing, coughing, or other close, personal contact. Pneumococcal pneumonia may begin suddenly, with a severe shaking chill usually followed by high fever, cough, shortness of breath, rapid breathing, and chest pains.

Pneumococcal lung infection begins when the pneumococcus is aspirated into the lung. Once in the lung, the microbe grows in the nutrient-rich edema fluid of the alveolar spaces. Neutrophils and alveolar macrophages then arrive to try to stop the infection. They are called into the area from the circulation by chemoattractant chemokines released by damaged alveolar cells. The thick polysaccharide capsule of the pneumococcus, however, makes phagocytosis very difficult (see Section

25.5). In an otherwise healthy adult, pneumococcal pneumonia usually involves one lobe of the lungs; thus, it is sometimes called lobar pneumonia. The infiltration of PMNs and fluid leads to the typical radiological findings of diffuse, cloudy areas. In contrast, infants, young children, and elderly people more commonly develop an infection in other parts of the lungs, such as around the air vessels (bronchi), causing bronchopneumonia.

The white blood cell count in the case history is telling. The patient had an elevated WBC count (normal is 5,000–10,000 per microliter) and an elevated proportion of band cells (normal is 0%–5%). These increases are indicative of a bacterial, not viral, infection. Neutrophils (PMNs), the front-line combatants against infection, rise in response to bacterial infections and are first released from bone marrow as immature band cells, whose presence is a sure sign of bacterial infection.

Outbreaks of pneumococcal pneumonia in nursing homes are not uncommon. Their residents' susceptibility to this disease underscores the importance of elderly people receiving the pneumococcal polysaccharide vaccine (PPSV23) as a hedge against infection. While there are over 80 antigenic types of pneumococcal capsular polysaccharides, the injected vaccine contains the 23 types that are most often associated with disease (see Section 24.6). This type of vaccine is called multivalent because it contains capsular antigens from multiple strains. The pneumococcal polysaccharide vaccine is recommended for individuals over age 65, as well as for those who are immunocompromised. The patient in this case history failed to receive the vaccine.

Children are also susceptible to *S. pneumoniae* and should be vaccinated, but children do not have a vigorous T cell–independent antibody response to polysaccharide antigens. To facilitate T-cell help, these patients are given a pneumococcal conjugate vaccine (PCV13), which contains capsular antigens from 13 serotypes of *S. pneumoniae* conjugated to a nontoxic variant of diphtheria toxin (see Chapter 24).

Thought Question

26.3 How does nontoxic diphtheria toxin (Dtx) conjugated to a capsular antigen facilitate T-cell help?

In addition to causing serious infections of the lungs, *S. pneumoniae* can invade the bloodstream (bacteremia) and the covering of the brain (meningitis). The death rates for these infections are about one out of every 20 who get pneumococcal pneumonia, about four out of 20 who get bacteremia, and six out of 20 who get meningitis. Individuals who are immunocompromised because of liver disease, AIDS (caused by HIV), or organ transplants are even more likely to die from the disease.

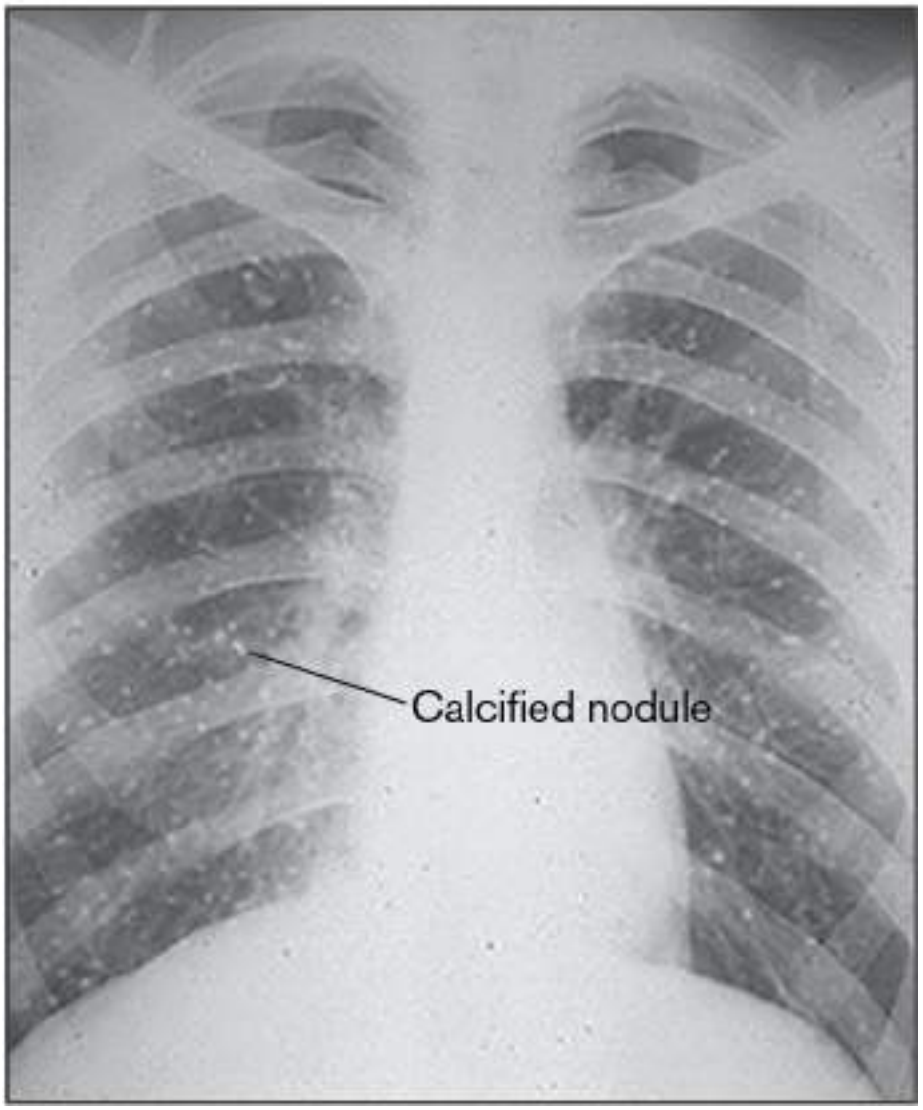
An emerging infectious disease problem throughout the United States and the world is the increasing resistance of *S. pneumoniae* to antibiotics. At least 30% of the strains isolated today are resistant to one or more antibiotics such as beta-lactams (penicillin) and macrolides (azithromycin). However, one consequence of vaccination is that the incidence of antibiotic-resistant isolates has been declining. Currently, amoxicillin can be used for penicillin-susceptible isolates, but third-generation cephalosporins (ceftriaxone) or fluoroquinolones are typically used to treat infections by antibiotic-resistant isolates. Chapter 27 discusses why antibiotic resistance is on the rise for this and other microbes.

Case History: Fungal Lung Infection

A 40-year-old salesman named Jaylen presented to an Ohio hospital emergency department with fever, cough, myalgias, and chest pain. One month earlier he had reported similar symptoms and had

been treated with azithromycin for suspected bacterial lung infection. His symptoms had not improved, and he now reported increasing weakness, difficulty breathing, abdominal pain, and a weight loss of 8 pounds in the previous month. While taking the patient's history, the physician assistant (PA) discovered that Jaylen is a weekend spelunker who frequently explores local caves and that he is bisexual, having had two male and three female partners in the previous year. Physical exam revealed enlarged cervical (neck) and axillary (armpit) lymph nodes (lymphadenopathy), lung congestion and hepatosplenomegaly (enlarged liver and spleen), and red, bumpy lesions on his legs. A complete blood count showed low numbers of red cells, white cells, and platelets (pancytopenia). A chest X-ray (***Fig. 26.9A*** *) showed small calcifications (opaque white areas) in both lungs. Suspecting tuberculosis, the PA administered a tuberculin skin test. The patient's symptoms and sexual history also dictated that serological tests for syphilis; hepatitis A, B, and C; and HIV be administered. Tests for tuberculosis, syphilis, and hepatitis were all negative, but Jaylen tested positive for HIV. His blood was cultured for the presence of bacteria and fungi.*

A.



B.

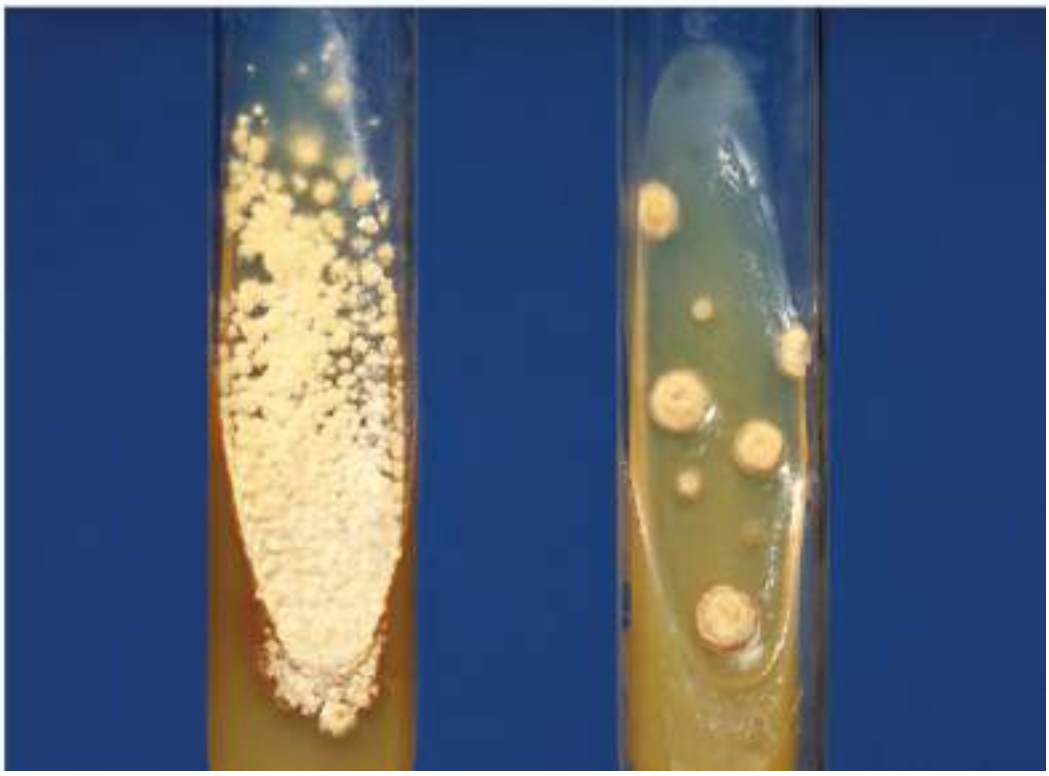


FIGURE 26.9 ■ Lung infection by *Histoplasma capsulatum* . A. X-ray of a patient with histoplasmosis. **B.** Colonies of *H. capsulatum* .

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GADO IMAGES/ALAMY STOCK PHOTO

This is a complicated though not unusual case. Health care providers often treat a patient for the most likely cause of the chief complaint, which in this case was a suspected bacterial lung infection. Azithromycin was prescribed, and the infection worsened. Antibiotic failure leading to a return visit forced a closer look. The flu-like symptoms and calcifications seen on the lung X-ray then suggested tuberculosis (another lung infection that can disseminate, discussed later). The negative skin test for tuberculosis, however, ruled out that disease, leaving fungus as the probable cause, given the chronic nature of the patient's symptoms. The infection in this patient probably started in the lung (clued by the cough), after which the organism spread throughout the body via the bloodstream to infect the liver and spleen.

Cryptococcus , an encapsulated yeast, is a potential cause. It typically requires an immunocompromised host to cause disease, and Jaylen's positive HIV test indicated he might be immunocompromised (he had a low CD4 T-cell count). *Cryptococcus* usually causes a brain infection, meningoencephalitis, but the organism can also infect the lungs, prostate gland, urinary tract, eyes, myocardium, bones, skin, and joints. The chest X-ray does not rule out *Cryptococcus* , because this yeast can cause similar images when infecting the lung. However, the pancytopenia is not typical of *Cryptococcus* , and a biopsy failed to find yeast cells with a thick capsule (example shown in **Fig. 26.10A**).

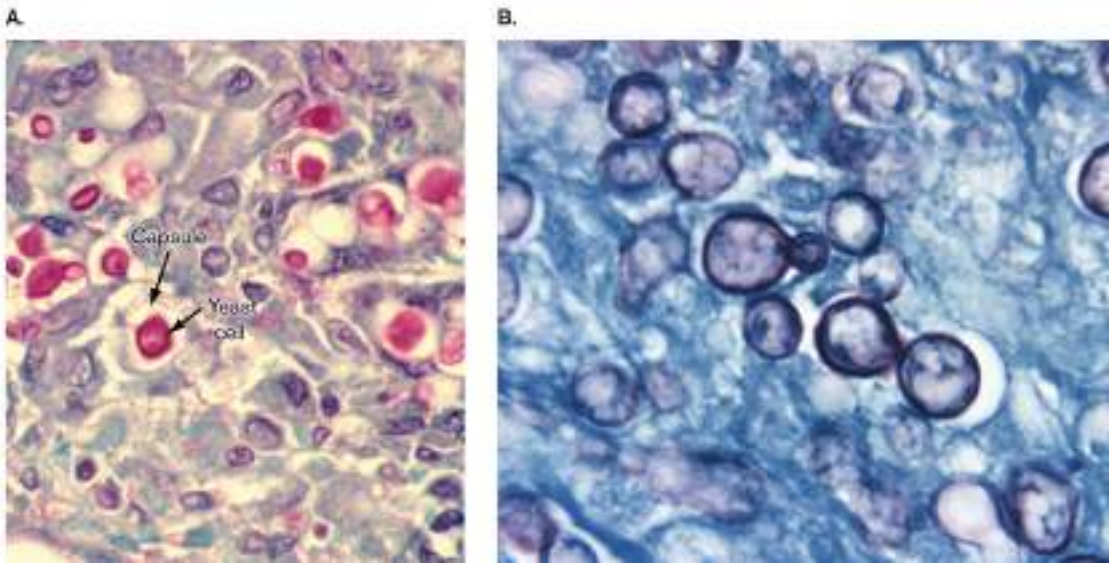


FIGURE 26.10 ■ *Cryptococcus neoformans* and *Histoplasma capsulatum* in lung biopsies. A. *C. neoformans* in lung nodule. Periodic acid–Schiff stain. **B.** *H. capsulatum* . Silver stain.

CDC/DR. EDWIN P. EWING, JR.
CDC/DR. LIBERO AJELLO

The most likely fungal causes of infection in this case history are the endemic mycoses, such as coccidioidomycosis, blastomycosis, and histoplasmosis. This patient had never traveled to the western United States, where coccidioidomycosis is endemic, so exposure to *Coccidioides* was ruled out. *Blastomyces dermatitidis* is a soil fungus endemic to the Ohio and Mississippi river valleys and the southeastern United States. The disease, blastomycosis, begins as a respiratory infection following the inhalation of conidia. From the lung, the organism can disseminate to the skin, bone, and genitourinary tract but rarely affects the liver or spleen, both of which were affected in Jaylen. Histoplasmosis, on the other hand, most commonly presents as a flu-like pulmonary illness that can progress to more serious pulmonary infection and can disseminate to the liver and spleen in severe cases.

On the basis of Jaylen's presentation and history of present illness, amphotericin B, a powerful antifungal agent (discussed in Section 27.5), was administered intravenously. The patient's fever lowered almost immediately. *Histoplasma* antigen was identified in his urine, and a fungus was found in the cultures of bronchoalveolar lavage fluid (lung washes; **Fig. 26.9B**). The fungus was definitively identified by a DNA probe and tissue biopsy as *Histoplasmosis capsulatum* (tissue biopsy in **Fig. 26.10B**), confirming the diagnosis of histoplasmosis.

Histoplasma is a dimorphic fungus that thrives in damp soil rich in organic material, especially the droppings of birds and bats. Dimorphic fungi take on a mycelial form at 25°C but grow as budding yeast at body temperature (37°C). Although *Histoplasma* is distributed worldwide, endemic areas in the United States include the Ohio and Mississippi river valleys (where Jaylen lives). People like Jaylen who explore caves populated by bats are at particular risk for contracting this disease, sometimes called cave disease. The infectious forms of *H. capsulatum* are microconidia (fungal spores) produced by differentiated mycelium. Jaylen did not wear a mask while spelunking and most likely inhaled a good number of spores while crawling through the caves.

The incubation period for histoplasmosis ranges from 3 to 17 days. Three general forms are recognized. In acute pulmonary histoplasmosis , immunocompetent patients are usually asymptomatic unless they inhale a large number of spores. If symptoms develop, patients typically display cold-like symptoms that can resolve within 3–4 weeks.

Chronic pulmonary histoplasmosis is a more serious manifestation, whose symptoms persist for at least 3 months. Symptoms include cough, dyspnea (difficulty breathing), fever, weight loss, malaise, and reddish, nodular skin lesions called erythema nodosum (a delayed-type hypersensitivity reaction to antigens from various infectious agents, including *Histoplasma*). Jaylen displayed all of these symptoms.

The most serious form of histoplasmosis, progressive disseminated histoplasmosis , includes dissemination to the spleen and liver (enlarging both) and is generally seen in patients who are immunocompromised because of corticosteroid use, organ transplant, or HIV infection. The pancytopenia seen in Jaylen is also common in this form of the disease (70%–90%). Jaylen tested positive for HIV and had a low CD4 T-cell count of 150 per microliter (normal is 500–1,500). Jaylen is immunocompromised. Because of his HIV status, Jaylen was also treated with antiviral agents to control his viral load. Lowering the viral load in his blood would allow his T-cell count to increase and improve his immunocompetence.

Several critical features of this case help differentiate it from the preceding case of pneumococcal pneumonia. First, the initial macrolide antibiotic, azithromycin, should have killed most bacterial sources of infection. Second, the X-ray finding of calcified pulmonary nodules is more indicative of fungal lung infection than of bacterial infection, which in a patient of this age would likely appear uniformly dense and confined to one lobe (see **Fig. 26.8A**). Tuberculosis would be an exception to this rule. Jaylen's blood count was also a clue. Fungal infections do not usually cause an increase in WBCs or an increase in band cells, as happens with pneumococcal pneumonia. The pancytopenia, however, is consistent with disseminated histoplasmosis. Note that many infectious diseases start out as a localized infection but end up disseminating throughout the body to cause new sites of infection.

Thought Question

26.4 Why isn't a dimorphic fungus like *Histoplasma* easily transmitted from person to person via respiratory droplets?

Tuberculosis as a Reemerging Disease

Tuberculosis (TB), caused by the acid-fast bacillus *Mycobacterium tuberculosis* (see Fig. 28.5), was the leading cause of death due to a single pathogen until the COVID-19 pandemic. Tuberculosis claimed 1.5 million lives worldwide in 2020, whereas COVID-19 claimed about 2 million, according to the World Health Organization. The death toll from tuberculosis is still shocking, considering that the disease was nearly eradicated in the developed world going into the 1980s. What happened?

The explosion in tuberculosis cases started shortly after the HIV pandemic arrived in 1985. Because HIV kills T cells, patients became immunocompromised and susceptible to many infections, including TB. By 1991, inner-city hospitals were beginning to see highly infectious multidrug-resistant (MDR) strains of *M. tuberculosis* that produced fulminant (rapid-onset) and fatal disease among patients infected with HIV (time from TB exposure to death was 2–7 months). Alongside the shocking rise in TB cases, U.S. health care workers exposed to TB patients had a tuberculin skin test conversion rate of 50%. (The tuberculin test is described in the next section.)

Tuberculin conversion rate is the percentage of tuberculin-negative health care providers who converted to tuberculin-positive over time, indicating exposure to *M. tuberculosis* . Today the rate is less than 0.5%. New cases of TB in the United States have decreased over the years (from 26,283 cases in 1991 down to 8,920 cases in 2019), but approximately 1.5% of the new cases are caused by MDR-TB. Despite progress reducing TB in developed countries, tuberculosis remains a leading cause

of global child mortality. Information about mycobacterial structure can be found in Section 18.3 , and mycobacterial pathogenesis is discussed in Section 25.5 .

Tuberculin skin test. The tuberculin skin test (also known as the Mantoux test) is the primary screen for tuberculosis. A mixture of *Mycobacterium tuberculosis* proteins (called purified protein derivative, or PPD) is injected under the skin of the lower arm. A person who has been infected will develop a localized delayed-type hypersensitivity reaction (a reddened area of skin with blisters) within 48 hours (see Chapter 24). Note, however, that a positive tuberculin skin test does not signify active disease, but only that the person was infected at one time. The bacterium may have been killed by the immune system without having caused disease or may lie dormant, waiting to reactivate. **Figure 26.11** outlines the disease course of untreated tuberculosis.

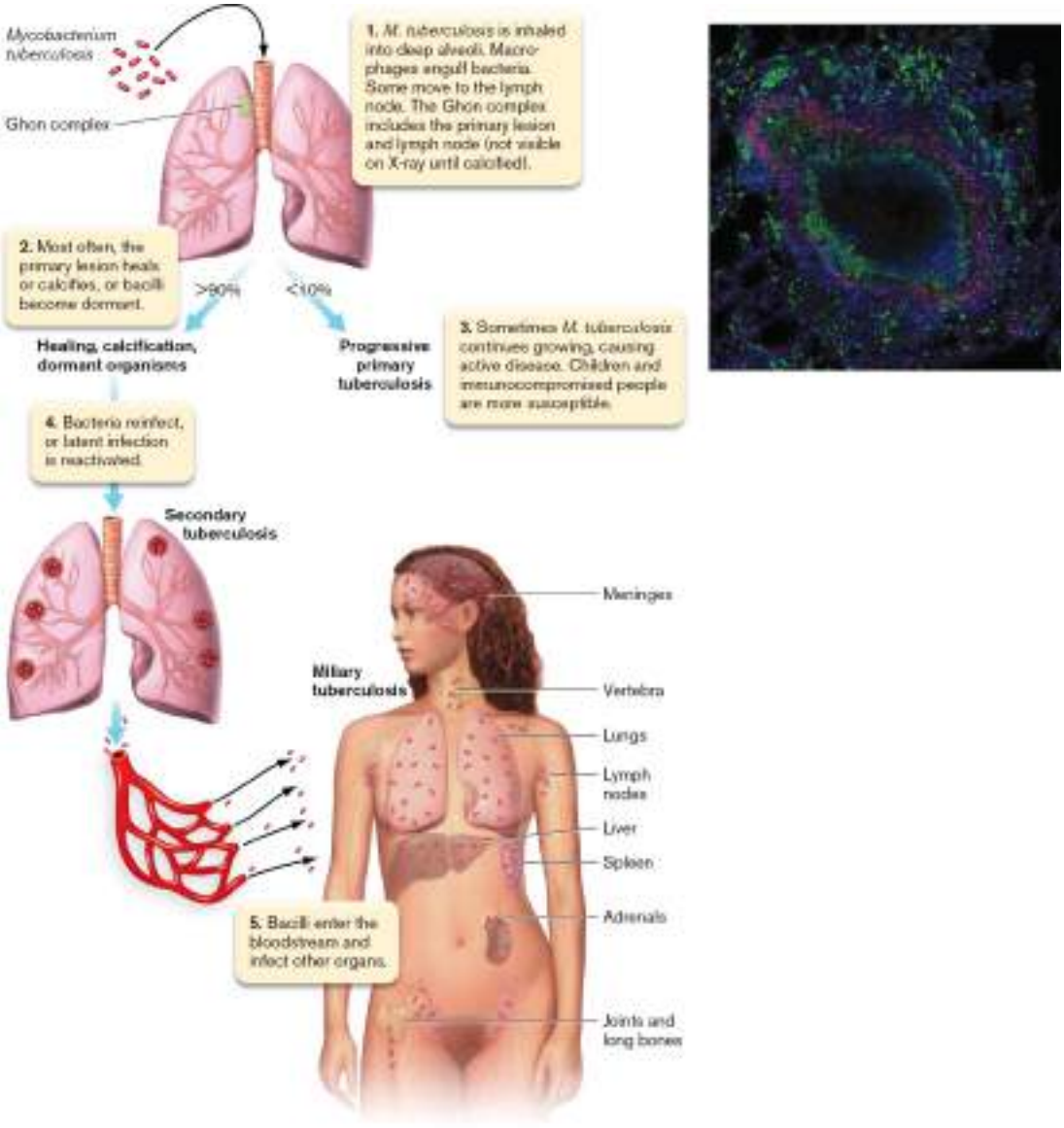


FIGURE 26.11 ■ The disease progression of tuberculosis. Step 1: The disease begins as primary tuberculosis. **Step 2:** Most patients never develop disease, or the organism becomes latent within granulomas. **Step 3:** A few patients develop progressive primary tuberculosis because the immune system failed to control the infection, leading to its spread to other lung

regions. **Step 4:** Secondary tuberculosis develops upon reinfection or reactivation of latent bacilli. **Step 5:** More damage occurs in the lung, and bacilli disseminate to other organs (including reseeding the lung) to produce miliary TB. **Inset:** TB granuloma in the lung of a nonhuman primate, stained with antibodies for CD31 T cells (red) and CD681 macrophages (green), surrounding a necrotic center (unstained). Cell nuclei are blue.
JOANNE L. FLYNN

Primary tuberculosis. Once inhaled into the lung, the bacilli deposit into alveoli and are subject to three possible outcomes (**Fig. 26.11** , steps 1 and 2): They can die, become latent, or produce progressive primary tuberculosis. In all three cases the bacteria are initially phagocytosed by alveolar macrophages, and a battle ensues. If the bacilli are not killed by the macrophages, the bacteria will survive ensconced within modified phagolysosomes, where they multiply and kill the macrophage via induced apoptosis. The bacilli are then free to infect other macrophages. The primary lesion is called a Ghon focus. During the pitched battle, some infected macrophages from the Ghon focus will travel to a regional lymph node of the lung. The Ghon focus and the infected lymph node are called the Ghon complex. However, the Ghon complex cannot be seen on an X-ray at this early stage. A delayed hypersensitivity develops, and these patients usually become tuberculin-positive.

The body reacts to bacilli in the lung by trying to wall them off in what is called a granuloma (**Fig. 26.11 inset**), a nodule (sometimes called a tubercle) containing macrophages (live and dead), plus other white blood cells and bacteria (live and dead). The inside of the granuloma can become necrotic with dead host and bacterial cells and develops the consistency of cheese—a process called caseation. Over time, calcium is deposited and the nodules become calcified. At this point, the hardened calcified nodules (Ghon complex) become visible on X-rays. Alternatively, the caseous center of the granuloma can liquefy and the bacilli multiply to large numbers. The granuloma can erode (cavitate) to release large numbers of bacilli into the bronchus. Coughing will expel the bacilli into the air for another person to inhale.

Four to six weeks after infection, about 10% of infected people will develop progressive (or active) primary disease in which bacilli in the primary focus grow and caseous material is disseminated to other parts of the lung (**Fig. 26.11** , step 3). Lung X-rays can show consolidation similar to pneumonia in this form of tuberculosis. Symptoms include a productive cough that generates sputum, fever, night sweats, and weight loss.

Secondary tuberculosis. As noted earlier, an alternative to primary disease is an asymptomatic latent tuberculosis infection (LTBI). Here the bacilli remain hidden in granulomas and may even become dormant, remaining so for many years. However, *M. tuberculosis* can sometimes overcome dormancy and escape confinement imposed by the immune system (**Fig. 26.11** , step 4). The bacteria begin to multiply and cause secondary tuberculosis . Secondary TB due to reactivation commonly occurs in immunocompromised people (such as HIV patients). Secondary tuberculosis can also be caused by the inhalation of new bacilli. Because these patients already developed cell-mediated immunity during primary infection, the symptoms of secondary TB are more serious than those of primary TB and include severe coughing, greenish or bloody sputum, low-grade fever, night sweats, and weight loss. The gradual wasting of the body is what led to the older name for tuberculosis: "consumption."

Extrapulmonary (miliary) TB. *Mycobacterium tuberculosis* bacilli in the lung can sometimes enter the pulmonary vein (**Fig. 26.11** , step 5). Once in the bloodstream, the organism will disseminate to produce abscesses in many different organ systems. Extrapulmonary TB is sometimes called miliary tuberculosis because the size of the infected nodules (1–5 mm), called tubercles, approximates the size of millet seeds. Miliary TB can develop during primary or secondary TB infections.

Treatment. Ten drugs are currently approved by the FDA for treatment of tuberculosis. Initial treatment of active disease is aggressive and involves a four-drug regimen of what are called first-line drugs (or drugs of choice)—namely, isoniazid, rifampin, pyrazinamide, and ethambutol—given over a course of several months. MDR strains (about 1% of total TB cases in the United States) are defined as being resistant to two or more first-line drugs. An MDR strain is treated with a regimen of four to five drugs that do not include the first-line drugs to which it is resistant. Extensively drug-resistant tuberculosis (XDR-TB) strains, as defined by the World Health Organization, are resistant to two or more first-line drugs, plus any fluoroquinolone and at least one second-line drug (bedaquiline, linezolid). XDR-TB strains are almost untreatable, although a recently approved drug called pretomanid is effective against XDR-TB. Pretomanid inhibits the biosynthesis of mycolic acid, a component of the *M. tuberculosis* cell wall. Although XDR-TB is rare in the United States, about 9% of MDR-TB strains worldwide are XDR-TB.

Thought Question

26.5 Explain why patient noncompliance (failure to take drugs as directed) is thought to have led to XDR-TB.

Case History: Viral Lung Infection

Felicia, a 57-year-old Black woman, presented to the emergency department in Tallahassee, Florida, in severe distress. Her symptoms included a 103° F fever, a severe but dry cough, fatigue, and dyspnea (difficulty breathing). Felicia's daughter explained that a week ago her mother awoke with a slight fever, headache, body aches, and a mild cough that had gotten progressively worse. Her daughter also mentioned that Felicia could not taste food. On arrival, Felicia's oxygen level by pulse oximeter was 78% (normal is > 92%), and a lung X-ray showed bilateral ground-glass opacities (**Fig. 26.12** *), a sign of viral pneumonia. Felicia was immediately admitted to the COVID-19 wing of the hospital. Her vaccination status was unknown* .



FIGURE 26.12 ■ Felicia's X-ray, showing inflammation in both lungs. The extensive ground-glass opacities (hazy gray areas throughout all lobes, as opposed to the consolidation observed in Fig. 26.8A) indicate a pneumonia that is typically (but not exclusively) of viral origin, such as coronavirus, influenza, measles, or respiratory syncytial virus.
ZARRINTAJ ALIABADI

Several viral diseases of the lung can produce symptoms and X-ray findings similar to those of Felicia. Examples include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza. However, the sudden loss of smell or taste that Felicia experienced is considered a hallmark of COVID-19, a disease caused by the SARS-CoV-2 virus (an enveloped, single-stranded, positive-sense RNA virus). The structure and replication of this virus are described in Section 6.5 . Here we discuss clinical features of COVID-19, including diagnosis, disease course, treatment, and prevention. Please recognize that as we write, the world was greeting 2022 mourning the loss of 5.4 million family members to COVID-19, including 800,000 in the United States. Sadly, it was not over.

Diagnosis. Diagnostic screening and confirmatory tests for COVID-19 include two nasal swab tests that look for a virus-specific antigen or a virus-specific RNA sequence. The third test involves testing blood for antiviral antibodies. The antigen test screens for the SARS-CoV-2 nucleocapsid [N] antigen, which can be detected 2–4 days after symptoms begin. The second and more sensitive nucleic acid test uses RT-PCR to look for N-gene RNA detectable at or just before symptoms start. The antibody blood test uses immunochromatography to find antispike or antinucleocapsid antibodies that form about a week after symptoms appear. Details of these kinds of tests are found in Chapter 28 . Felicia and her daughter tested positive by the antigen and the RT-PCR tests. The daughter, however, never developed symptoms.

Because most people who feel well do not seek testing, no one really knows how many SARS-CoV-2–infected but asymptomatic people there have been. However, estimates place the number at about 80% of those infected. It is important to remember that although these people are not ill, they

still shed virus and can infect others. Why some infected people become seriously ill or die while most are asymptomatic or develop only mild disease is not completely understood. However, people who are immunocompromised by comorbidities such as obesity, hypertension, or diabetes are most susceptible to developing severe COVID-19. People over age 65 account for 75% of COVID-19 deaths.

Clinical course. Transmission of the virus is mainly person to person via respiratory droplets or aerosols. There is a risk that the virus can be transmitted indirectly via contaminated inanimate objects, but the risk is slight. Early measures in 2020 to slow transmission included self-quarantining, the use of masks, and avoiding crowds. Compliance, however, was not universal, so the virus spread quickly. From January 19, 2020 (the first U.S. case), until October 2020, 7 million people in the United States tested positive for the virus, and 205,000 died. As of November 2021, nearly 800,000 Americans had died, and the world as a whole had experienced 5.2 million deaths. By the time you read this, many more will have succumbed.

Upon initial infection, one of the first tasks of the virus is to prevent the host from producing interferon, which would limit viral replication. As a result, adults easily become infected by the virus. Children, however, are more resistant to infection, probably because they are more efficient than adults at producing protective interferons in their upper respiratory tract (see Section 23.5).

On average, symptoms appear about 5 days after infection. Clinical outcomes range from symptomatic, as mentioned, to mildly or severely ill. The initial site of infection is the lung, primarily via ciliated cells and alveolar epithelial cells that possess ACE2 receptors. Spike proteins of the virus attach to ACE2 receptors on lung cells to gain entry. Replication is described in Chapter 6 (Figures 6.27 and 6.28). Once replicating in the lung, the virus can disseminate via the bloodstream and infect ACE2-containing intestinal cells and cardiovascular endothelial cells—leading, respectively, to diarrhea or cardiac injury in some patients. The liver and kidneys also contain ACE2 receptors and can become damaged through direct infection.

In addition to direct infection, excessive inflammation triggered by a virus-induced cytokine storm (see Section 24.3) will produce serious conditions such as acute respiratory distress syndrome (ARDS), thromboembolism, heart arrhythmias, and renal failure. The most dangerous form of the disease, severe acute COVID-19, can develop after a week of mild to moderate symptoms. Then, just as the patient may think they are recovering, an unbalanced immune host response develops that ruthlessly damages organ systems and can lead to death. Felicia, in our case, developed severe acute COVID-19, was placed on a ventilator, and received antiviral monoclonal antibodies as well as dexamethasone to combat inflammation (see below). Eventually, she recovered, whereas so many others did not.

Multisystem inflammatory syndrome. Although children are less susceptible to developing COVID-19, some who are infected develop a serious version called multisystem inflammatory syndrome in children (MIS-C) , in which a child with current or past infection (within 4 weeks of onset) becomes feverish and shows signs of inflammation in various organ systems. Such signs include chest pain or dizziness (heart), trouble breathing (lung), reduced urine output (kidney), confusion (brain), rash (skin), bloodshot eyes, or diarrhea (GI). In rare cases, adults have developed a similar condition referred to as MIS-A. With medical care, most adults and children with this syndrome eventually recover.

Post-acute sequelae of SARS-CoV-2 infection. PASC, also known as long COVID, is defined as having symptoms that linger for weeks or months after a patient begins to recover. About 10% of people with COVID-19 get long COVID. Symptoms include "brain fog," fatigue, loss of smell and taste, cough, joint pain, or chest pain. The cause is unclear, but recent evidence indicates that unusual levels of cytokines and autoantibodies may be involved.

Treatment. At first, treatment of COVID-19 was limited to supportive methods such as using IV fluids or vasopressors to maintain blood pressure, ventilators to maintain airflow, and powerful,

broad-acting corticosteroids such as dexamethasone to limit inflammation in severely ill patients (still used today). Effective antiviral drugs were unavailable. Fortunately, accelerated research produced new, highly targeted, and effective treatments. For example, SARS-CoV-2 IgG monoclonal antibodies (mAbs) were designed to target various sites on the viral spike protein to block virus attachment to ACE2 receptors, essentially neutralizing the virus. The two monoclonal preparations, sotrovimab (made by GlaxoSmithKlein) and REGEN-COV (made by Regeneron), were effective against early forms of the virus and were used to treat mild to moderate disease. Unfortunately, these monoclonal antibodies are no longer prescribed because they were ineffective against newer variants such as Omicron or its subvariants (discussed below). Newer monoclonal antibodies that will neutralize those variants are under investigation. Despite this setback, other monoclonal antibodies that act as immunomodulators remain effective. Tocilizumab, for instance, binds to the receptor for the cytokine interleukin-6 (IL-6), a major pro-inflammatory instigator of the vascular dysfunction leading to COVID pneumonia.

New oral antivirals include a protease inhibitor (Paxlovid by Pfizer) and a cytosine nucleoside analog (molnupiravir, originally developed by Merck to treat influenza). When used within 5 days of the onset of symptoms, both drugs can significantly reduce the chances of high-risk patients developing severe COVID-19: Paxlovid by 90%, molnupiravir by 30%. Paxlovid inhibits two viral proteases needed to process viral proteins into their functional forms. Without this processing, infectious virus cannot be formed. In contrast, a metabolite of molnupiravir causes the RNA-dependent RNA polymerase of the virus to introduce so many mutations in the viral genome that the progeny cannot survive. (These antiviral mechanisms are described in Chapter 27 .) Both of these drugs are effective against the variants of SARS-CoV-2, such as Omicron and its subvariants (described next), that escape the immune responses elicited by the COVID-19 vaccines. Both drugs received emergency use approval by the FDA in December 2021.

Prevention and SARS-CoV-2 variants. The remarkable mRNA vaccines developed by Moderna and Pfizer (described in Section 16.6) significantly stemmed the COVID-19 pandemic in the United States and throughout the world. Unfortunately, as of April 2022, only 66% of the U.S. population had been fully vaccinated. As a result, new cases and deaths continued, primarily among the unvaccinated. The data in **Figure 26.13** illustrate how the pandemic in the United States progressed in waves, where daily case numbers increased and waned, only to increase again. This pandemic's cyclical nature can be attributed to many reasons, including the loss of vaccine effectiveness over time; careless adherence to public health measures such as mask wearing, social distancing, and hand washing; and mutational changes taking place as the virus continues to replicate and evolve in unvaccinated people (see eResearch Activity 25). However, evidence indicates that the vaccines stimulate T-cell memory that can cross-recognize variants up through Omicron, partially explaining why vaccinated individuals are less likely to develop serious COVID-19 symptoms with those variants.

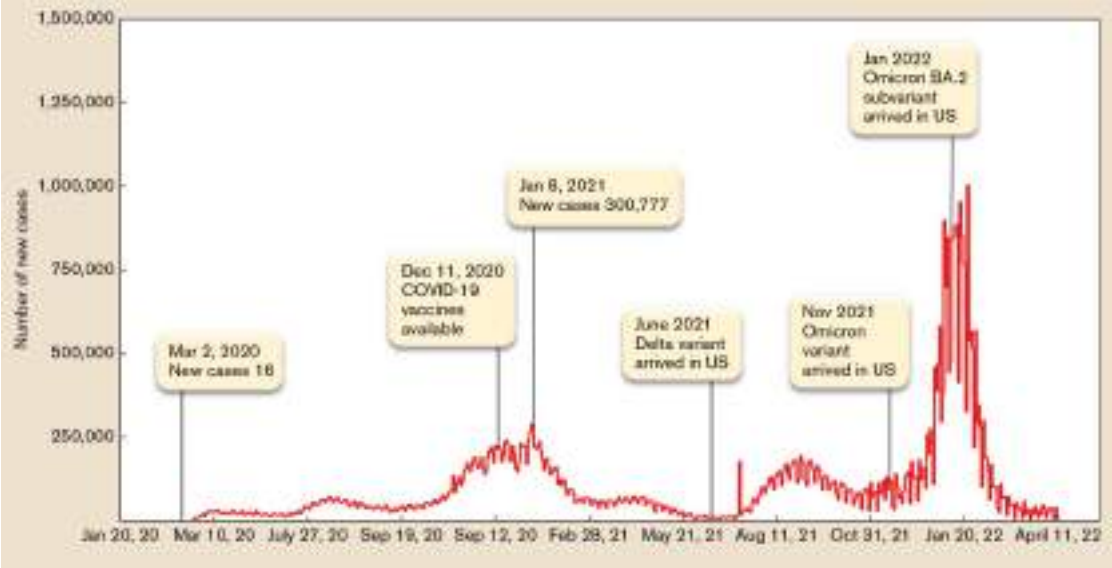
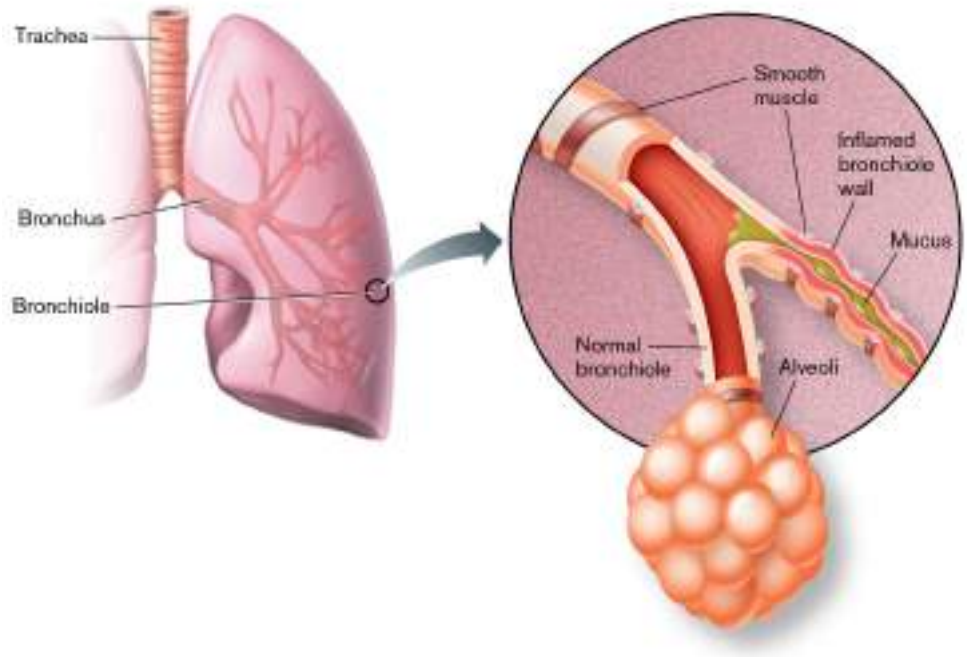


FIGURE 26.13 ■ COVID-19 pandemic cases in the United States. Data show positive tests on each day.

The wave beginning in October 2020 was caused by lax adherence to public health measures as people gathered indoors over the holidays. The number of cases dropped after the vaccine became available in December 2020. But a subsequent rise starting in June 2021 developed once the SARS-CoV-2 Delta variant arrived in the United States. The Delta variant, which originated in India, has several mutations, two of which occur in the spike protein gene. The Delta variant was more transmissible than the original and partially resistant to the available vaccines.

Late in 2021, a new, heavily mutated variant called Omicron emerged from Africa and spawned a number of even more highly transmissible, but less virulent, subvariants such as BA.2. As with the Delta variant, the available vaccines were not as effective against the Omicron variants. Efforts to tailor the mRNA vaccines toward these new variants were underway as of April 2022.

Respiratory syncytial virus. Another important viral lung infection is respiratory syncytial disease, caused by respiratory syncytial virus (RSV). A negative-sense, single-stranded RNA enveloped virus, RSV is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age (**Fig. 26.14**).



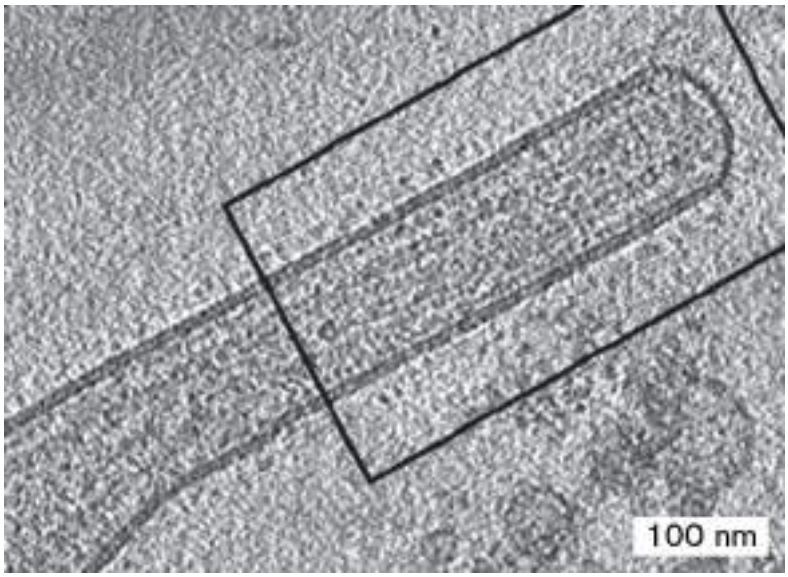


FIGURE 26.14 ■ Respiratory syncytial virus is the major cause of bronchiolitis in children. Location of RSV infection in the lung. Inflammation and excess mucus impair breathing. **Inset photo:** TEM of the linear form of RSV. Circular forms also occur.
KISS ET AL. 2014. *J. VIROL.* **88** :7602–7617, FIG. 1A.

Illness begins most frequently with fever, runny nose, cough, and sometimes wheezing. RSV is spread from respiratory secretions through close contact with infected persons or by contact with contaminated surfaces or objects. Infection can occur when the virus contacts mucous membranes of

the eyes, mouth, or nose and possibly through the inhalation of droplets generated by a sneeze or cough. Unlike rubella or rubeola, which infect the respiratory tract and disseminate through the body, RSV remains localized in the lung.

The majority of children hospitalized for RSV infection are under 6 months of age. RSV can cause repeated infections throughout life, usually associated with moderate to severe cold-like symptoms. Severe lower respiratory tract disease may occur at any age, especially among the elderly or people with compromised cardiac, pulmonary, or immune systems. As yet, a vaccine to control this disease is not available. However, a monoclonal antibody called palivizumab, which binds to an RSV epitope, can prevent RSV infection in high-risk infants who were born either prematurely or with medical problems such as congenital heart failure.

Table 26.2 presents many other bacterial, fungal, and viral microbes that can cause respiratory tract infection. Be aware that very different diseases can produce similar symptoms. For instance, people constantly confuse influenza (the flu) with the common cold. Symptomatically, they may start out similarly, but there are telling differences. Influenza is characterized by fever, myalgia (muscle aches), pharyngitis (sore throat), and headache (viral infection is discussed in Chapter 11). A runny nose is not one of the symptoms. The common cold, however, manifests as a runny nose, nasal congestion, sneezing, and throat irritation. No myalgia. The observant clinician will note the difference.

To Summarize

- **Most lung infections are viral** , but most deadly lung infections are caused by bacteria.
- **The mucociliary escalator** is a primary defense mechanism used by the lung to avoid infection.
- **An elevated white cell count** in blood is an indicator of bacterial infection.
- **Pneumococcal vaccine** should be administered to the elderly because they are often immunocompromised.
- **Fungal agents** commonly cause long-term, chronic infections.
- **Localized bacterial infections in the lung can disseminate** via the bloodstream to form lesions at other body sites.
- **Tuberculosis** is an ancient bacterial disease with an increasing mortality rate resulting from multidrug-resistant strains, the susceptibility of HIV patients, and an increasing indigent population.
- **COVID-19, caused by SARS-CoV-2 virus** , begins as a lung infection but can disseminate via blood to other organ systems. The virus can initiate a life-threatening, out-of-control inflammatory response (cytokine storm) capable of damaging many organ systems.
- **Respiratory syncytial virus** is one of several viruses that can cause lung disease, but it rarely spreads to other organs.

Glossary

granuloma
: A thick lesion formed around a site of infection.

secondary tuberculosis
: A new round of serious disease that is caused by *Mycobacterium tuberculosis* in patients with latent tuberculosis who have become immunocompromised. Symptoms include severe cough, blood sputum, night sweats, and weight loss.

multisystem inflammatory syndrome in children (MIS-C)

A systemic multi-organ inflammatory syndrome in children brought on by COVID-19 disease.
Fig. 28.5

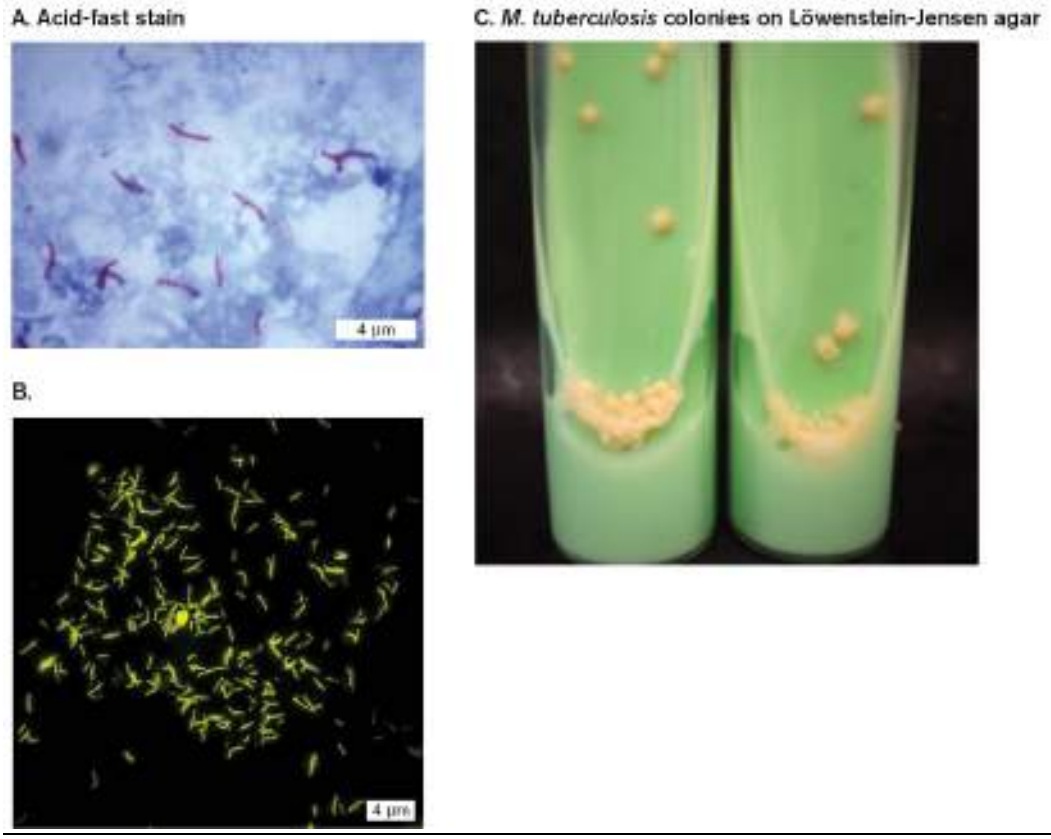


FIGURE 28.5 ■ Acid-fast stain and growth of *Mycobacterium tuberculosis* . A. Acid-fast Ziehl-Neelsen stain of *M. tuberculosis* . **B.** Auramine O fluorescent acid-fast bacilli (AFB) stain. **C.** Löwenstein-Jensen medium enables growth of mycobacterial species, some of which grow extremely slowly. The colonies have a "bread crumb–like" appearance.
CDC
SITTIPONG SREECHAT/© 123RF.COM
AGARWAL, S., ET AL. 2005. *ANN CLIN MICROB ANTI* **4** (18)

Figure 6.27

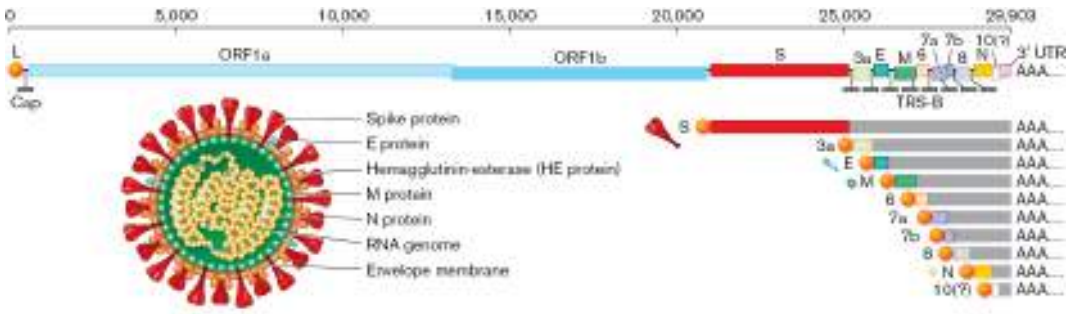


FIGURE 6.27 ■ SARS-CoV-2 virion structure and genome. ORFs (open reading frames) and genes are shown staggered where translation begins in a different reading frame (triplet start position) from that of the adjacent upstream gene. The (+) strand RNA genome has a eukaryotic cap (7-methyl-Gppp) attached at the 5′ end (indicated as orange

ball). Within the host cell, all genome copies and mRNA molecules have a cap attached by the host cell's capping enzyme. 3′ UTR = 3′ untranslated region; AAA = 5′ poly-A tail.

Figure 6.28

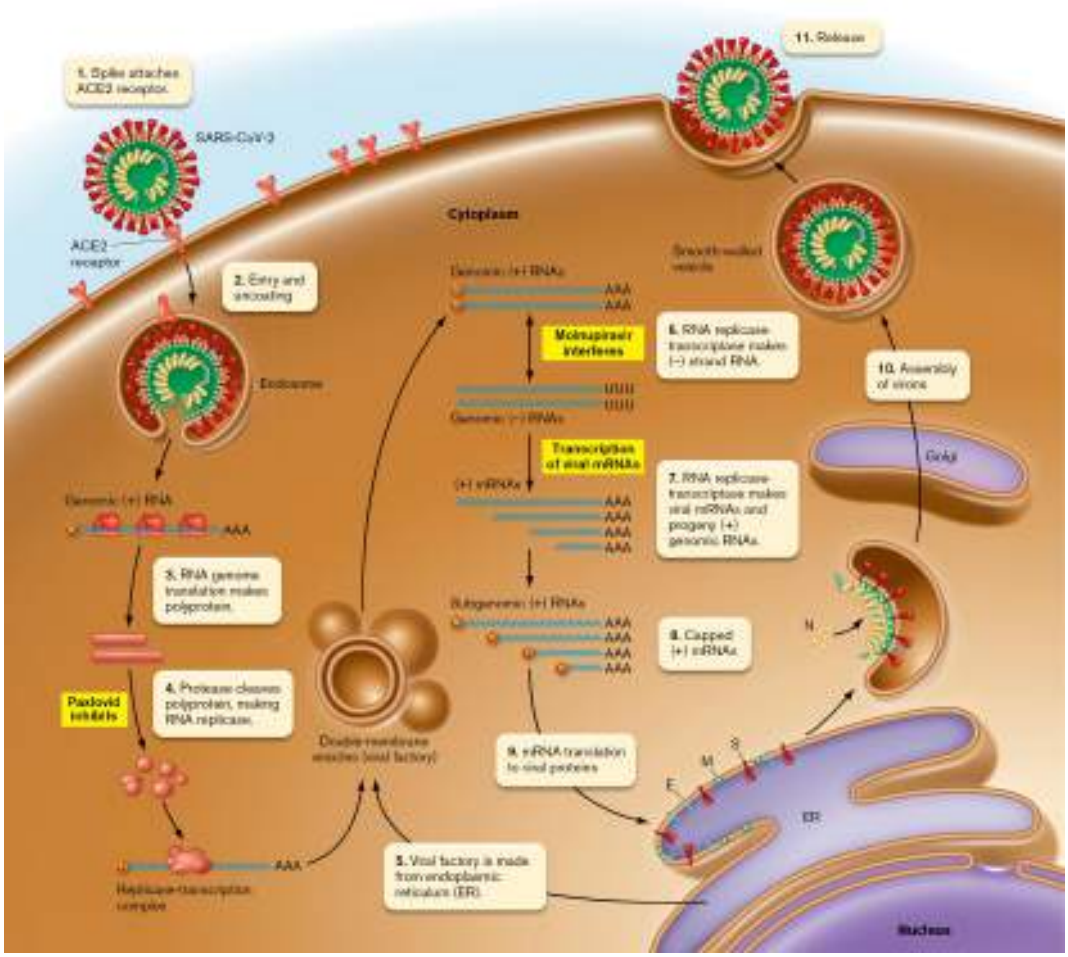


FIGURE 6.28 ■ SARS-CoV-2 replication cycle. The virion binds the ACE2 receptor. It then undergoes endocytosis and uncoats in the host cytoplasm. The released RNA genome is translated by host ribosomes to synthesize the RNA-dependent RNA polymerase (replicase). The replicase synthesizes (−) strand RNA, which serves as a template for transcription to mRNAs. Endoplasmic reticulum (ER) membrane becomes transformed into viral factories (double-membrane vesicles) that organize virion assembly and transport to the Golgi complex. From the Golgi, virions move to the cell membrane and bud out.

Endnotes

1. Note a: Formerly genus *Chlamydophila* but has been changed back to *Chlamydia* . Return to reference a
2. Note a: Formerly genus *Chlamydophila* but has been changed back to *Chlamydia* . Return to reference a

3. Note b: BCG = Bacille Calmette-Guérin (a weakened strain of the bovine tuberculosis strain). Return to reference b
4. Note c: Palivizumab = monoclonal antibody to RSV protein. Return to reference c

26.3 Gastrointestinal Tract Infections

Nearly everyone has experienced diarrhea, a condition characterized by frequent loose bowel movements accompanied by abdominal cramps. Hundreds of millions of cases occur each year in the United States and are a major cause of death in developing countries. As with respiratory tract infections, most diarrheal disease is viral in origin, with rotavirus being the primary culprit. Among the bacteria, the Gram-negative rod *Salmonella enterica* serovar Typhimurium and the spiral-shaped or curved bacillus *Campylobacter* are the most frequent causes of self-limiting diarrheal disease.

You might wonder why some microbes, like *Campylobacter jejuni* (**Fig. 26.15**), prefer the chaos of diarrhea to the relative stability of a nice commensal relationship. After all, isn't finding a niche and sticking to it the goal of every microbe? The simple answer is that diarrhea enables the dissemination of microbes that might otherwise kill their host or be killed themselves by too aggressively provoking the host's immune system. Dissemination into the environment enables the microbe to reach new hosts and proliferate. A diarrhea-causing microbe is rather like a serial bank robber fleeing from city to city to avoid capture and find more banks to rob.

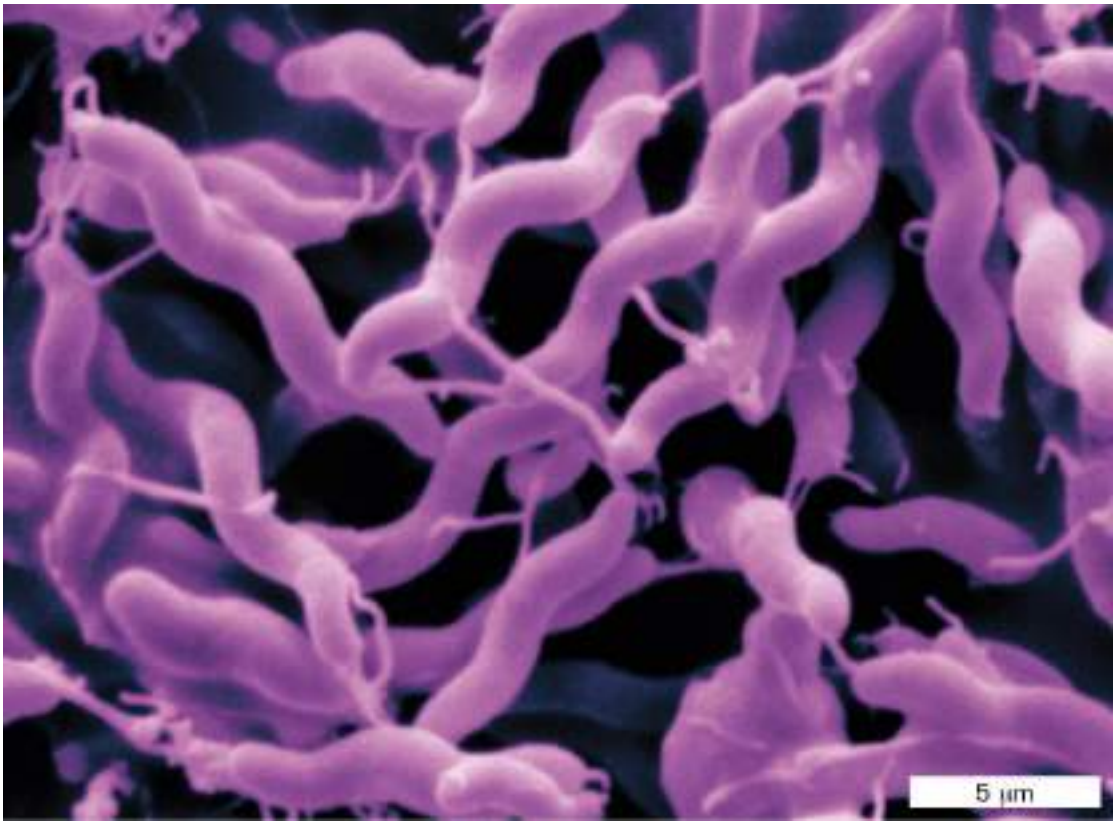


FIGURE 26.15 ■ Campylobacter jejuni (SEM). This Gram-negative, spiral-shaped bacterial pathogen (cell length 5 µm) is a major cause of human diarrhea. Symptoms of *C. jejuni* infection include cramps, fever, and bloody diarrhea. Animals, such as chickens and other birds raised for meat and their eggs, are the usual reservoirs for this pathogen, so it is considered a zoonotic disease. Transmission is typically via ingestion of contaminated water or undercooked poultry.
MEDISCAN/ALAMY STOCK PHOTO

Types of Diarrhea

What causes diarrhea? Normally, intestinal mucosal cells absorb water (8–10 liters per day) from the intestinal contents, essentially drying out stool. Diarrhea occurs when water is not absorbed or when it actually leaves intestinal cells and enters the intestinal lumen. The excess water loosens stool, and diarrhea results. There are several types of diarrhea:

- **Osmotic diarrhea** happens when nonabsorbable substrates, such as lactulose, a synthetic sugar, are used to treat constipation. Lactulose increases osmolarity in the intestine, causing water to leave mucosal cells. Infectious organisms (such as rotavirus) that prevent nutrient absorption can cause osmotic diarrhea.
- **Secretory diarrhea** develops when microbes cause mucosal cells to increase ion secretion, as seen with cholera toxin. Mucosal cells expel water to try to equilibrate the resulting electrolyte imbalance.
- **Inflammatory diarrhea** forms when an infectious agent triggers the production of inflammatory cytokines that attract PMNs. Subsequent damage to the intestinal wall limits water and nutrient absorption and causes red and white blood cells to enter the stool (bloody diarrhea or dysentery). *Shigella* , *Salmonella* , and some strains of *E. coli* can cause inflammatory diarrhea.
- **Motility-related diarrhea** can develop when enterotoxins made by pathogens such as rotavirus cause intestinal hypermotility. Food moves through the intestine too fast for water or nutrients to be absorbed.

Terms used to describe the inflammation of different parts of the GI tract include:

- **Gastritis** (inflammation of the stomach lining—for instance, ulcers).
- **Gastroenteritis** (nonspecific term for any inflammation along the gastrointestinal tract).
- **Enteritis** (inflammation mainly of the small intestine).
- **Enterocolitis** (inflammation of the colon and small intestine).
- **Colitis** (inflammation of the large intestine—colon).

Rehydration therapy. Diarrhea and vomiting due to viral growth, bacterial growth, or toxin production can cause large amounts of water to leave the intestinal cells and enter the intestinal lumen. As a result, the patient can become dangerously dehydrated. Most deaths resulting from infectious diarrhea are the result of dehydration. Consequently, the most important treatment for diarrhea is rehydration therapy . But giving water alone is not enough. Water leaving tissues causes an osmotic imbalance that compels electrolytes to exit too (as a way to reestablish balance). The resulting electrolyte imbalance severely affects cardiovascular, respiratory, and renal systems, leading to systemic failure, which is the real cause of death. Giving water alone will only make the electrolyte imbalance worse. Therefore, rehydration solutions must also contain glucose, as well as sodium and potassium salts in proper balance (for example, Pedialyte).

Antibiotics are often inappropriate when treating diarrhea. Although antibiotic treatment of infectious gastroenteritis seems intuitive, it is rarely used and actually contraindicated. Most gastrointestinal infections are viral (norovirus or rotavirus), so antibiotics are ineffective. Likewise, gastroenteritis caused by bacteria usually resolves spontaneously without antibiotic treatment. However, severe systemic disease stemming from gastroenteritis can develop, often in the young or elderly. Diseases like bacillary dysentery (*Shigella dysenteriae*) respond well to antibiotics.

In some cases, antibiotic treatment can actually trigger gastrointestinal disease. For example, many antibiotics used to treat infectious diseases can kill most normal intestinal bacteria, except the naturally resistant Gram-positive, spore-forming anaerobe *Clostridioides difficile* (formerly *Clostridium difficile*), the causative agent of pseudomembranous enterocolitis. Unrestrained by microbial competition, *C. difficile* growing at the epithelial surface of the intestine will produce specific toxins that damage and kill intestinal cells. The organism's growth leads to inflammation and the formation of exudative plaques along the intestinal wall (refer to Fig. 23.11D). The plaques eventually coalesce into larger pseudomembrane structures that block the intestinal mucosa. The blockage causes the malabsorption of nutrients and water, resulting in diarrhea. As the pseudomembrane enlarges, it begins to slough off and pass into the stool. Diagnosis of this disease involves PCR identification of the organism or immunological identification of the toxin in fecal samples.



Some patients suffer recurrent *C. difficile* infections. It is not clear why, but one suggestion is that spores lodged in colon folds may escape clearance by peristalsis. Another hypothesis is that patients with recurrent disease have an impaired response to the *C. difficile* toxins. How can recurrences be prevented? In some instances, after vegetative *C. difficile* has been killed by antibiotic treatment, a procedure known as a fecal transplant (see Section 23.2) can be used to restore a healthy gastrointestinal microbiome that prevents the recurrence of *C. difficile* disease.

Staphylococcal Food Poisoning

We have all heard of a local church picnic or a restaurant where scores of people become violently ill within hours of eating unrefrigerated potato salad or other food. *Staphylococcus aureus* is the usual cause of these disasters, but it is not an infection. The culprit is an enterotoxin (an exotoxin that affects the gastrointestinal tract) secreted by some strains of *S. aureus* into tainted foods such as pies, turkey dressing, or potato salad. After ingestion, the toxin travels to the intestine, where it enters the bloodstream and stimulates the vagus nerve leading to the vomit center in the brain.

Because the toxin is preformed, symptoms occur quickly after ingestion. Within 2–6 hours, the poisoned patient will begin vomiting and may also experience diarrhea. The disease, though violent, is not life-threatening and usually resolves spontaneously within 24–48 hours. In contrast, diarrhea caused by infectious agents such as *Salmonella enterica* , which must first grow in the victim, does not occur until 12–24 hours after ingestion and sometimes longer. A clinician noting quick onset of symptoms in a patient will immediately suspect staphylococcal food poisoning. Obviously, antibiotic treatment is not needed for staph food poisoning, but it may be indicated for other gastrointestinal infections. Staphylococcal enterotoxins are also heat resistant, so simply heating a food already containing enterotoxin will not destroy the toxic activity.

Case History: Enterohemorrhagic *E. coli*

Tammy, a 6-year-old girl from Montgomery County, Pennsylvania, arrived at the ER with bloody diarrhea, a temperature of 39°C (102.2°F), abdominal cramping, and vomiting. She was admitted to the hospital 5 days after a kindergarten field trip to the local dairy farm. When questioned about Tammy's activities during the trip, her parents said she had purchased a snack while at the farm. A fecal smear analyzed in the laboratory was positive for leukocytes and, when cultured on a sorbitol MacConkey agar plate, produced sorbitol-nonfermenting colonies suspected of being enterohemorrhagic E. coli *O157:H7. PCR tests confirmed this suspicion, identifying the presence of genes for Shiga toxins 1 and 2 and the* eae *gene encoding intimin (see Chapter 25). Meanwhile, Tammy had developed additional problems. Her face and hands had become puffy, her urine output had decreased despite being given IV fluids (suggesting kidney damage), and she was beginning to develop some neurological abnormalities. Laboratory analyses of blood samples revealed thrombocytopenia (reduced blood platelet count) and confirmed hemolytic uremic syndrome (HUS; renal failure). Tammy was treated by IV fluid and electrolyte replacement. Antibiotics were not administered. She eventually recovered.*

In this case history, the presence of leukocytes in a fecal smear is a sign that the intestinal pathogen may have invaded the epithelial mucosa of the intestine (or severely damaged it). Breaching this barrier sends out a chemical call (chemokine) to neutrophils, which then enter the area and, in an effort to kill the pathogen, also damage the intestinal cells. *Shigella dysenteriae* , *Salmonella enterica* , and enteroinvasive *E. coli* (EIEC) actually invade enterocytes and are considered intracellular pathogens. Enterohemorrhagic *E. coli* (EHEC), which also produces leukocytes and blood in stools, is not an intracellular parasite (it is not invasive) but causes damaging attachment and effacing lesions, described in Section 25.4 that destroy the mucosal epithelium. The resulting inflammation, in conjunction with damage caused by the Shiga toxin it produces, leads to blood and white cells in the stool. *E. coli* O157:H7, the etiological agent in the case history, is a common serotype of EHEC.

There are at least seven different classes (pathovars) of pathogenic *E. coli* , differing in their repertoire of pathogenicity islands, plasmids, and virulence factors. They include the enteroinvasive (EIEC) and enterohemorrhagic (EHEC) pathovars just mentioned, plus the enterotoxigenic *E. coli* (ETEC), neonatal meningitis-causing *E. coli* (NMEC), uropathogenic *E. coli* (UPEC), enteropathogenic *E. coli* (EPEC), and enteroaggregative *E. coli* (EAEC). All but UPEC and NMEC cause gastrointestinal disease. To distinguish these strains, each group has telltale O and H antigens that can be identified by using serology or PCR to identify allelic differences in genes encoding LPS synthesis.

Note: "O antigen" is part of the bacterium's LPS, while "H antigen" is a flagellar protein. Thus, "O157:H7" denotes the specific versions of LPS (O157) and flagellar protein (H7) found on *E. coli* O157:H7. Other pathogenic strains of *E. coli* have different O and H antigens.

Shiga toxin. *Shigella* and EHEC, the agent in the preceding case history, both produce toxins, called Shiga toxins 1 and 2, that are encoded by genes of bacteriophage genomes (prophages) embedded in the bacterial chromosome. The toxins, which are absorbed through the intestine and disseminated via the bloodstream, are AB5 toxins (see Section 25.3). The A subunit, upon entry, destroys protein synthesis by cleaving an adenine from 28S rRNA in eukaryotic ribosomes. These toxins inhibit host protein synthesis and, in the process, damage endothelial cells in the intestine, kidney, and brain. Shiga toxin–induced death of vascular endothelial cells in the intestine causes the breakdown of blood vessel linings, followed by hemorrhage that manifests as bloody diarrhea. Shiga toxin 2 also triggers the release of pro-inflammatory cytokines.

Endothelial damage initiates the formation of platelet-fibrin microthrombi (clots) that occlude blood vessels in the various organs, leading to two major syndromes: hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). HUS develops when the microthrombi are limited to the kidney. The microclots clog the tiny blood vessels in this organ and cause decreased urine output, ultimately leading to kidney failure and death. In TTP, the clots occur throughout the circulation, causing reddish skin hemorrhages called petechiae and purpuras (discussed in Section 25.3). Neurological symptoms (for example, confusion, severe headaches, and possibly coma) then arise from microhemorrhages in the brain. The hemorrhaging occurs because platelets needed for normal clotting have been removed from the circulation as they form the microthrombi. The decreased number of platelets is called thrombocytopenia.

HUS is a common consequence of *E. coli* O157:H7 infection, as in the case history described. Unfortunately, HUS can be treated only with supportive care, such as blood transfusions and dialysis throughout the critical period until kidney function resumes. Antibiotic treatment can increase the release of Shiga toxins from the organisms and actually trigger HUS. Thus, antimicrobial therapy is not recommended.

Enterohemorrhagic *E. coli* (EHEC). *E. coli* O157:H7 is a recently emerged pathogen that can colonize cattle intestines at the recto-anal junction without affecting the animal and, as a result, can contaminate meat products following slaughter. Initially identified in 1982, the organism came to national prominence during a large-scale U.S. outbreak in 1993, linked to a Washington State Jack in the Box restaurant, in which 732 people were sickened.

E. coli O157:H7 rarely affects the health of the reservoir animal. But when an infected steer is slaughtered, the carcass can become contaminated with EHEC-containing feces despite considerable efforts by slaughterhouses to prevent it. Grinding the tainted meat into hamburger distributes the microbe throughout. Cooking burgers to 160°C is essential to kill any existing EHEC. Cross-contamination between foods is possible too. Using the same cutting board to prepare meat and salad is a great way to contaminate the salad, which will not be cooked.

Despite EHEC's common association with hamburger, vegetarians are not safe from this organism. During heavy rains, waste from a cattle farm can easily wash into nearby vegetable fields unless precautions are taken. If the cattle waste contains *E. coli* O157:H7, the crops become contaminated,

and the pathogen can enter the plant through stomates (respiration openings in the leaves; **Fig. 26.16**). One such outbreak occurred in 2018 when romaine lettuce grown in certain areas of Yuma, Arizona, was contaminated with this pathogen. Lettuce shipped to 36 states infected 210 people. Of those, 96 were hospitalized, 25 developed HUS, and 5 died. Whole-genome sequencing genetically linked all of the isolated EHEC strains to various farms in Yuma and identified the likely source as water from a canal in the Yuma growing area.

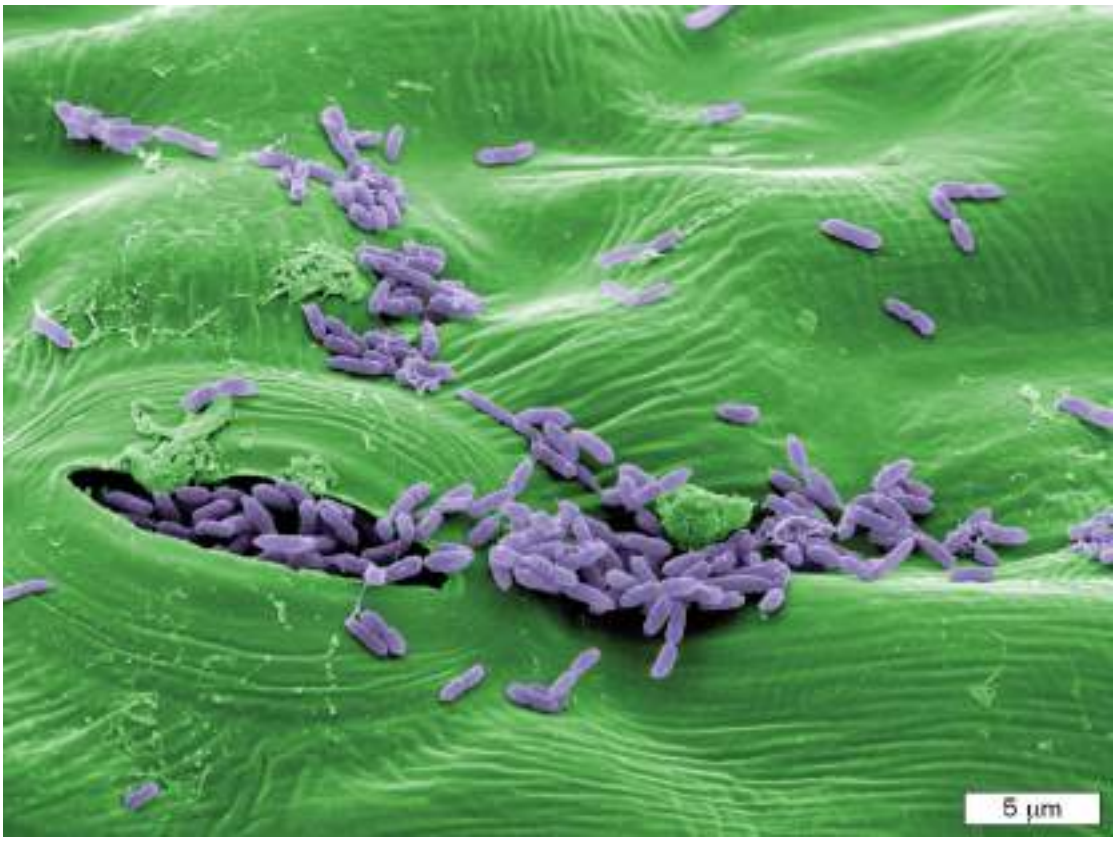


FIGURE 26.16 ■ *E. coli* entering a lettuce leaf. *Escherichia coli* individuals on a lettuce leaf congregate at the stomates and enter the plant veins. Once inside the plant, the organisms resist efforts to wash them out.
SCIMAT/SCIENCE SOURCE

Early on, the remarkably low infectious dose of *E. coli* O157:H7 mystified researchers. However, we have since learned that *E. coli* has an impressive level of acid resistance, rivaling that of the gastric pathogen *Helicobacter pylori* . Acid resistance mechanisms permit *E. coli* to survive in the acidic stomach and enable a mere 10–100 individual organisms to cause disease.

In contrast to the case just described, many gastrointestinal infections do not produce fecal leukocytes or blood in the stool. Diarrheal diseases caused by *Vibrio cholerae* (cholera) or enterotoxigenic *E. coli* (ETEC), which produces a cholera-like disease, do not involve invasion of the intestinal lining by the microbe, and they yield copious amounts of watery diarrhea. In these two toxin-driven diseases, the bacteria attach to cells lining the intestine and secrete toxins that are imported into the target cells (see Section 25.3).

How can we prevent disease caused by enterohemorrhagic *E. coli* ? Industry approaches include thoroughly washing carcasses before processing, maintaining cold temperatures, and testing for possible contamination. In addition, the use of gamma irradiation to sterilize beef, spinach, and lettuce has been approved. Outbreaks of EHEC disease caused by contaminated hamburger have declined

dramatically because of industry practices and USDA inspections. Irradiation (described in Chapter 5) could eliminate the problem, but less than 5% of hamburger meat is currently irradiated in the United States.

Rotavirus and Norovirus

Many people wrongly think that most cases of diarrhea are caused by a bacterial agent. Actually, two viruses—namely, rotavirus and norovirus —cause more intestinal disease than do any bacterial species. Rotavirus is a double-stranded RNA virus (Group III in Table 6.2); norovirus is a positive-sense, single-stranded RNA virus (Group IV). Rotavirus is highly infectious, spreading by the fecal-oral route; it is endemic around the globe, and it affects all age groups, although children between 6 and 24 months are the most severely affected. It is estimated that by age 3, all children have had a rotavirus infection.

The incubation period is approximately 2 days, after which the victim commonly suffers frequent watery, dark green, explosive diarrhea. Accompanying symptoms may include nausea, vomiting, and abdominal cramping. Severe dehydration and electrolyte loss due to the diarrhea will cause death unless supportive measures, such as fluid replacement, are undertaken. There is no cure, but most patients recover if rehydrated properly. Few deaths from rotavirus occur in the United States, but each year 120,00 to 250,00 children worldwide die from this viral diarrhea (2021 estimate). The mortality and incidence of this disease have decreased because of the introduction in 2006 of a safe and effective vaccine (see Table 24.5). In Mexico alone, the vaccine resulted in a 50% decline in diarrheal deaths.

With the success of the rotavirus vaccine, norovirus is set to become the most common worldwide cause of nonbacterial gastroenteritis. Norovirus infections have already surpassed rotavirus in the United States. The virus is perceived as the scourge of cruise ships and assisted-living facilities, but norovirus can also spread quickly in hotels or anywhere there are many people in a small area. The virus spreads by the fecal-oral route among children or adults, via contaminated food or person-to-person contact. Within 24 hours of infection, the victim experiences sudden vomiting, stomach cramps, and watery diarrhea that mercifully resolves within 12–24 hours. Treatment is similar to that for rotavirus, but there is no vaccine. Death is rare, but when it does occur, it is most common among infants and the elderly. Take notice that newly emerging single-stranded, positive-sense viruses in a group called sapoviruses are now causing increasing cases of norovirus-like disease (1%–17% of diarrhea episodes worldwide).

Note: Norovirus infection is sometimes called the "stomach flu," but that is a misnomer. It is not the flu and has nothing to do with influenza virus.

Diarrhea and the gut microbiome. An obvious question to ask about diarrhea is: How does it affect the microbiome? A study headed by Shannon Manning (Michigan State University) found that the composition of intestinal microbiota of patients with diarrhea differs significantly from those of their healthy family members.



For one thing, the gut microbiomes of diarrhea patients who were not given antibiotics were less diverse than those of their uninfected family members. Abundance of Bacteroidetes and Firmicutes was higher in the healthy individuals, whereas Proteobacteria dominated the patient microbiomes. *Escherichia coli* , for instance, predominated in all patients, regardless of the pathogen causing the infection. The composition of diarrheal microbiomes also varied with the bacterial cause of infection. As one example, the microbiome of *Campylobacter* -infected patients differed from that of patients infected with *Salmonella* or *Shigella* .

How does the intestine restore its bacterial population after being decimated by diarrhea or antibiotic treatment? Lawrence David (Duke University; **Fig. 26.17A**) and Peter Turnbaugh (UC San

Francisco), along with their colleagues, used metagenomic procedures to characterize the stools of 41 people in Bangladesh (children and adults) who had diarrhea caused by *E. coli* or *Vibrio cholerae* . Stools were monitored before, during, and after diarrhea episodes.

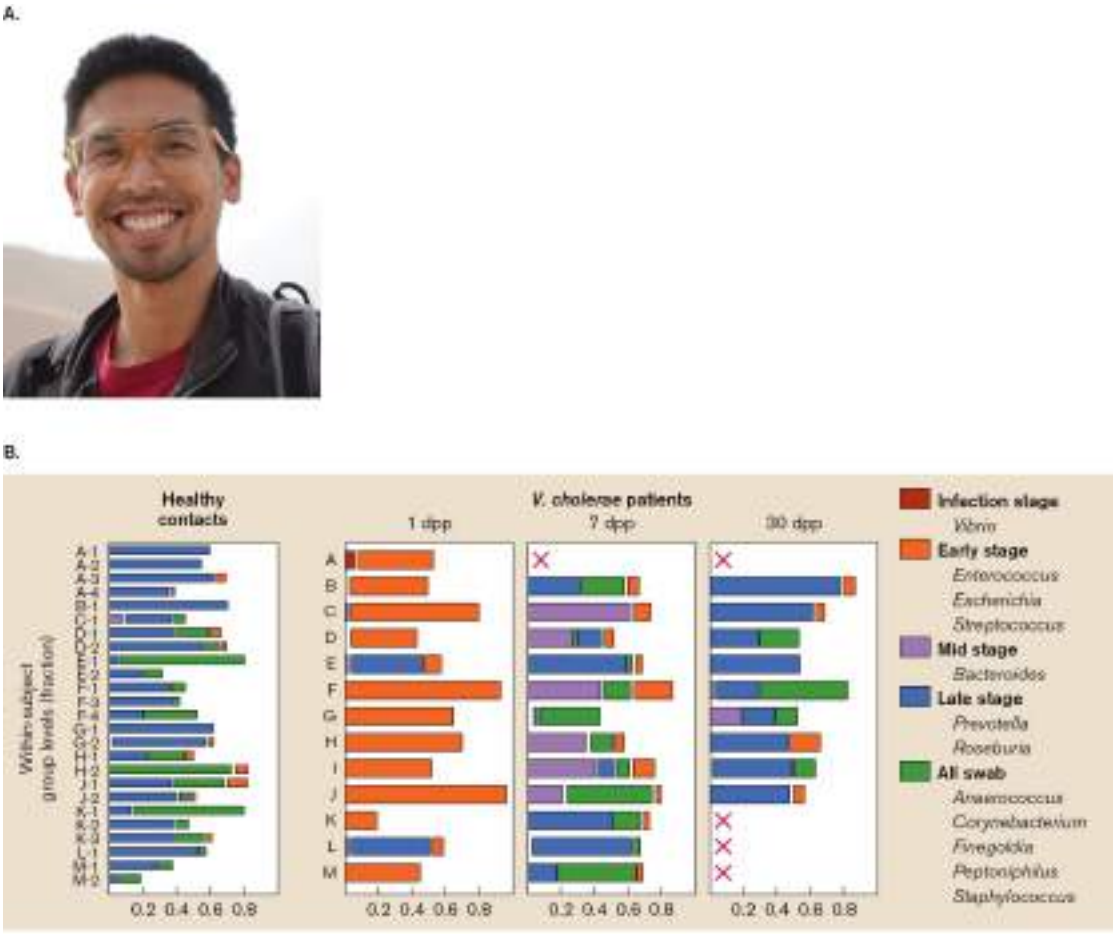


FIGURE 26.17 ■ Successive repopulation of the gut microbiome following *Vibrio cholerae* infection. A. Lawrence David (pictured) and Peter Turnbaugh (not shown) unravel the complexities of the human microbiome. **B.** Fecal samples were taken at 1, 7, and 30 days past presentation (dpp) of diarrhea. Patients, identified by letters, were given a single dose of azithromycin on the day of presentation, which nearly eliminated *V. cholerae* by 1 dpp. Healthy contacts of each patient are identified by numbers and are shown on the left. For example, A-1, A-2, A-3, and A-4 are the healthy contacts of patient A. Colored boxes reflect groups of different genera that are prominent during the infection and afterward, during early, mid, and late stages of repopulation. The *x* -axis values reflect relative abundances of genera. "All swab" microbes were present only in rectal swab samples.

Source: Part B modified from Harvard Press Office figure.
COURTESY OF LAWRENCE DAVID

The researchers identified a consistent succession of repopulation events in nearly every case, regardless of the cause of diarrhea (**Fig. 26.17B**). After diarrhea clears out much of the microbiome (either naturally or after antibiotic treatment), carbohydrates and oxygen accumulate in the gut. Carbohydrates and oxygen would normally be metabolized by gut microbiota. During the early stage of repopulation, facultative, oxygen-respiring, and carbohydrate-utilizing bacteria (especially those using

simple carbohydrates, such as *Escherichia* , *Enterococcus* , and *Streptococcus*) colonize the gut and consume these nutrients. Midstage recovery begins when the lack of simple sugars and oxygen (as well as increased phage predation) leads to a decline in the early-stage species. This decline enables succession to anaerobic, complex carbohydrate-fermenting bacteria (*Bacteroides*). Finally, in late-stage recovery, the gut microbiome once again resembles the complex community that existed prior to infection—that is, the same composition seen in healthy contacts (**Fig. 26.17B**). The entire process takes about 30 days to complete but depends on a variety of factors, such as diet, antibiotic use, and duration of diarrhea.

Repopulation occurs, in part, by microbes being reingested from food. But exciting research suggests that the much maligned and trivialized appendix is, among other things, an important reservoir of gut microbes that can seed the intestine and reestablish the microbiota. Once properly reestablished, gut microbiota are capable of fending off pathogens such as *Clostridioides difficile* . As evidence, researchers found that patients with appendectomies were more than twice as likely to develop repetitive infections with *C. difficile* . eResearch Activity 26 presents additional intriguing evidence that, during a transient infection, the gut microbiome "learns" how to better protect its host against a subsequent GI (gastrointestinal) infection.

Case History: Ulcers—It's Not What You Eat

Gary was a 34-year-old accountant who had immigrated to Nebraska from Poland 7 years earlier. Since his teenage years, he had been bothered periodically by episodes of epigastric pain (pain around the stomach), nausea, and heartburn. Antacids usually alleviated the symptoms. Over the years, he had received several courses of treatment with Tagamet or Pepcid to reduce acid secretion and provide relief. Recently, an upper-GI endoscopy had been performed, in which a long, thin tube tipped with a camera and light source was inserted into Gary's mouth and threaded down into his stomach. The view through the endoscope showed some reddened areas in the antrum (bottom part) of the stomach. The endoscope was also equipped with a small clawlike structure that obtained a small tissue sample from the lining of Gary's stomach. A urease test performed on the antral biopsy turned positive in 20 minutes. Histological examination of the biopsy confirmed moderate chronic active gastritis (inflammation of the stomach lining) and revealed the presence of numerous spiral-shaped organisms. Cultures of the antral biopsy were positive for Helicobacter pylori.

Painful and sometimes life-threatening gastric ulcers were for many years blamed on spicy foods and stress. In the 1980s, after discovering odd, helical bacteria present in the biopsies of gastric ulcers, Australians J. Robin Warren and Barry Marshall (a medical intern at the Royal Perth Hospital at the time; **Fig. 26.18A**) proposed that bacteria, not pepperoni, cause ulcers (**Fig. 26.18B** and **C**).

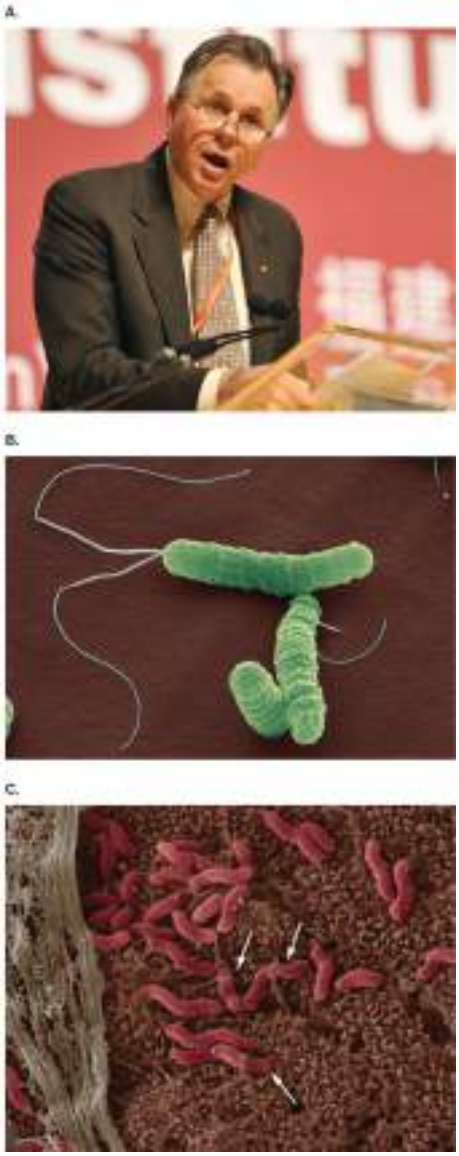


FIGURE 26.18 ■ A bacterial cause of gastric ulcers. A. Physician Barry Marshall was so sure he was right about the cause of stomach ulcers that he swallowed bacteria to prove his point. **B.** *Helicobacter pylori* (SEM). Note the tuft of flagella at one pole. Cell length approx. 2 μm. **C.** *Helicobacter* (arrows) attached to gastric mucosa.

XINHUA/ALAMY STOCK PHOTO
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Their hypothesis was viewed with skepticism and derided as heresy by the established medical community. Faced with disbelief bordering on ridicule, the young intern drank a vial of the helical organisms and waited. A week later he began vomiting and suffered other painful symptoms of gastritis. Barry Marshall could not have been happier. He had proved his point. We now know that this curly microbe causes the vast majority of stomach ulcers and has colonized humans for at least 100,000 years.

The discovery of *Helicobacter pylori* and its association with gastric ulcer disease led to a major shift in ulcer treatment, previously limited to suppressing acid production via proton pump inhibitors. Therapy now includes antimicrobial treatment to kill the bacteria, coupled with acid suppression

therapy to prevent further inflammation while the ulcer heals. Warren and Marshall, who recovered from his gastritis, received the 2005 Nobel Prize in Physiology or Medicine for their groundbreaking work.

H. pylori can be detected in about half of the world's population, especially in impoverished countries. Why most people colonized with *H. pylori* do not develop gastric ulcers is unclear. The exact mechanism by which *H. pylori* causes gastric ulcers is not known, although a variety of virulence factors have been identified. The basic scheme of *Helicobacter* pathogenesis is shown in **Figure 26.19** . After the pathogen is ingested, *H. pylori* flagella propel the organism toward the mucosa, driven by an ill-defined chemotaxis system that, in part, senses urea produced by the human body (**Fig. 26.19** , step 1). As it approaches the mucosa, the pathogen produces intracellular and extracellular urease, an important virulence factor that converts urea to CO_2 and ammonia. The ammonia neutralizes acid around *Helicobacter* , thereby enabling the organism to survive the extreme acidity of the stomach (step 2).

Two other enzymes—namely, collagenase and mucinase—then soften the mucous lining, helping the bacteria reach the stomach's epithelial lining (**Figs. 26.18C** and **26.19** , step 3). The epithelial lining is much less acidic than the lumen, so the organism can grow and divide. Once at the epithelium, *Helicobacter* produces various adhesins, such as BabA or HpaA, to bind host cells (step 4). After the organism has adhered, tissue damage develops with the release of vacuolating cytotoxin (VacA) and neutrophil-activating protein (NAP). NAP activates neutrophils and mast cells to damage local tissue (step 5). VacA forms a hexameric pore in the host membrane and induces apoptosis (programmed cell death) by damaging mitochondria. Apoptotic cells decrease the immune response, which will stabilize a chronic infection.

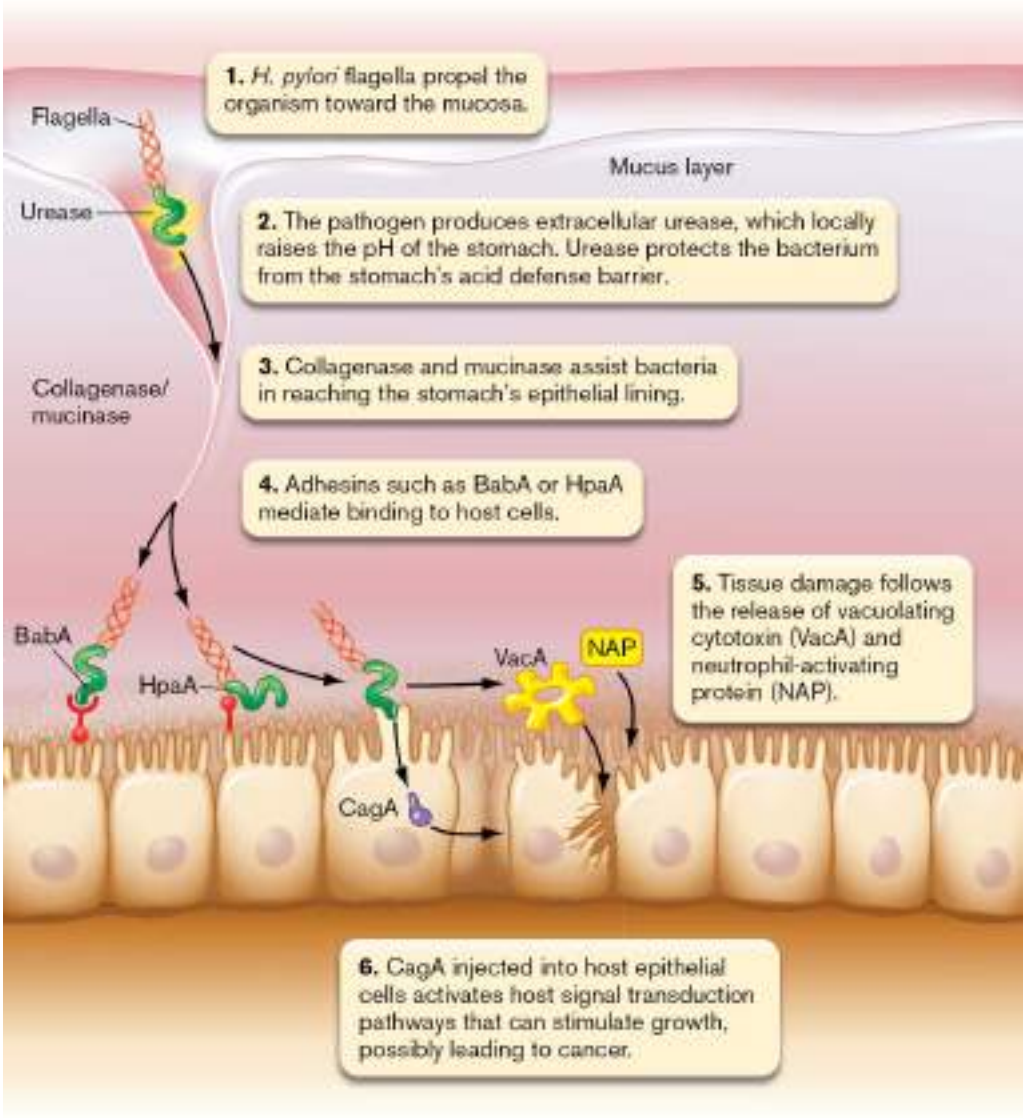


FIGURE 26.19 ■ Steps in *Helicobacter* pathogenesis.

Another protein, CagA, is injected (by a type IV secretion system; see Chapter 25) into host epithelial cells, where it becomes phosphorylated. CagA then interacts with host signaling proteins and activates host signal transduction pathways that can stimulate inflammation and growth possibly leading to cancer (**Fig. 26.19** , step 6). Gastric adenocarcinoma is the third leading cause of cancer deaths worldwide, and *Helicobacter* is a leading cause of gastric cancer.

Evidence continues to suggest that *H. pylori* can affect diseases outside the stomach. CagA, for example, has been found in patient serum, packaged within exosome vesicles generated by host exocytosis. *Helicobacter* also sheds outer membrane vesicles (OMVs) that contain CagA. OMVs containing CagA incubated with host cells produced changes in host cell gene expression and function. Recent data suggests the CagA exosomes can damage endothelial cells of the cardiovascular system.

Tools useful for diagnosing *H. pylori* include a fecal antigen test, rapid urease testing, and serology [for example, enzyme-linked immunosorbent assay (ELISA) to detect antibody to the CagA antigen]. ELISA is a common immunological tool used to detect the presence, in serum, of antibodies to a

specific organism, which are an indication of infection. The ELISA test is described more fully in Section 28.3 .

Protozoan Causes of Diarrheal Disease

As we learned in Chapter 20 , some protozoa (also called protists) cause serious human diseases. For instance, *Entamoeba histolytica* (**Fig. 26.20A** and Section 20.6) and *Cryptosporidium* (*C. parvum* and *C. hominis* ; **Fig. 26.20B**) cause the diarrheal diseases amebic dysentery and cryptosporidiosis, respectively. The CDC estimates (2018) that there are about 750,000 cases of cryptosporidiosis each year in the United States but that less than 2% are reported because many cases are mild or asymptomatic. *Cryptosporidium* infection begins with oocysts that contain four sporozoites (infectious form of protozoan) being shed in the feces of infected hosts (human and nonhuman animals) to contaminate water (drinking or recreational, such as in water parks). Following ingestion, the sporozoites are released and parasitize intestinal epithelial cells. Asexual and sexual cycles then lead to more oocysts. Treatment of immunocompetent patients usually involves only rehydration therapy, although an antiparasitic drug (nitazoxanide) is available. HIV patients infected with *C. parvum* must also receive antiretroviral therapy to improve CD4 T-cell count.

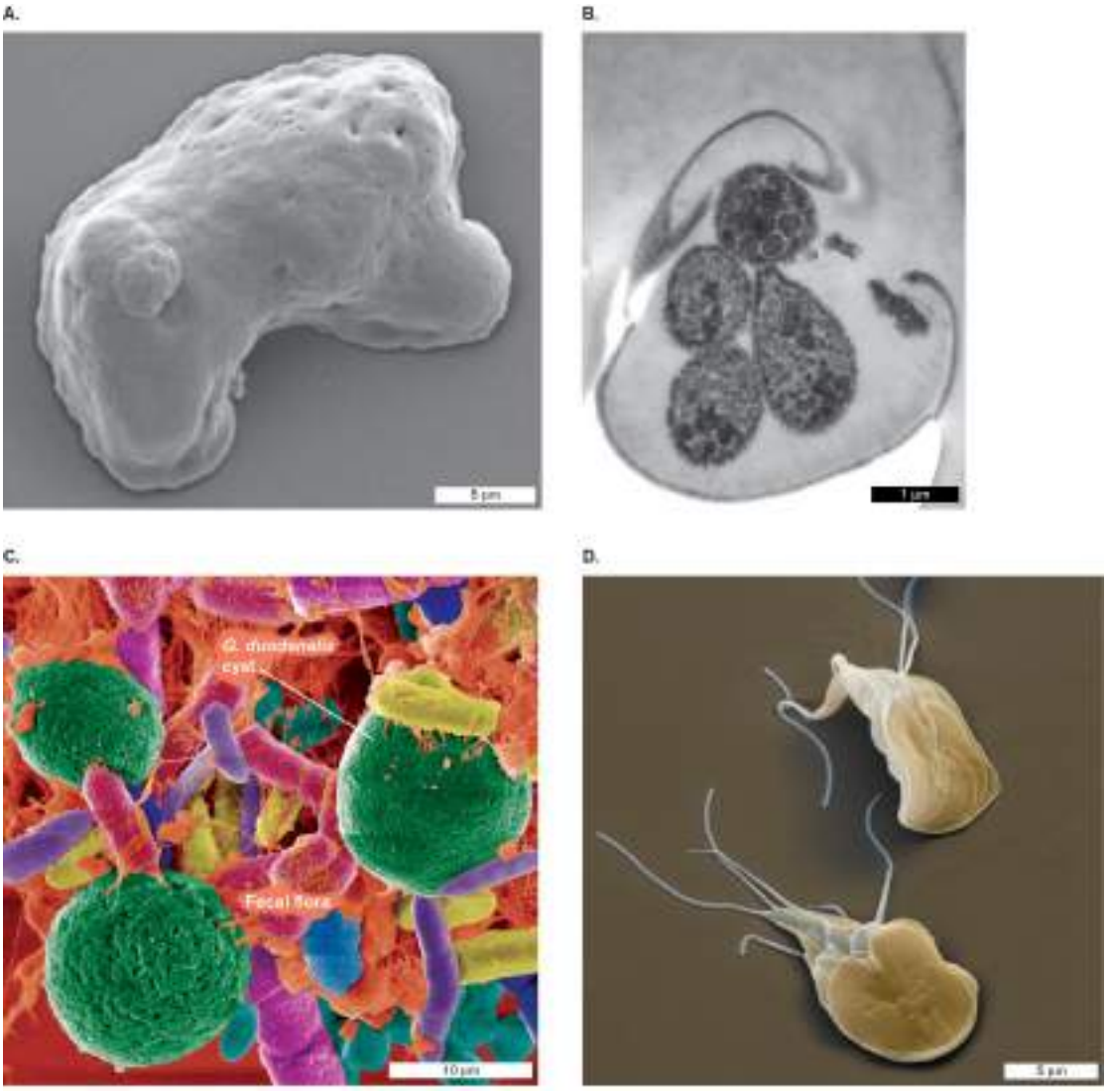


FIGURE 26.20 ■ Protists that cause diarrhea. A. *Entamoeba histolytica* trophozoite (SEM, motile form). **B.** *Cryptosporidium parvum* oocyst encasing four infectious sporozoites (TEM). **C.** *Giardia duodenalis* cysts (7–14 µm) present in fecal matter (colorized SEM). **D.** Trophozoite form of *G. duodenalis* (5–15 µm in length; colorized SEM).

AVALOS-PADILLA ET AL. 2015. *PLOS PATHOG.* **11** :E1005079, FIG. 8A.
ALDEYARBI AND KARANIS. 2016. *EUR. J. PROTISTOL.* **52** :36–44, FIG. 1A.
DR. GARY GAUGLER/SCIENCE SOURCE
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The flagellated protozoan *Giardia duodenalis* (formerly G. lamblia or intestinalis) is a major cause of diarrhea throughout the world. In the United States alone, *G. duodenalis* is thought to cause over 1 million illnesses per year. *G. duodenalis* enters a human or other host as a cyst present in drinking water contaminated by feces (**Fig. 26.20C**). A cyst is a dormant form of a protist encased in a protective wall (see Chapter 20). Aside from humans, *G. duodenalis* can be found in various rodents, deer, cattle, and even household pets. It is very infectious. Ingestion of as few as 25 cysts can lead to disease. Following ingestion, the hard outer coating of the cyst is dissolved by the action of digestive juices to produce a trophozoite (**Fig. 26.20D**), which attaches itself to the wall of the small intestines and reproduces. Offspring quickly encyst and are excreted out of the host's body.

Asymptomatic carriers of *G. duodenalis* are common; it has been estimated that anywhere from 1% to 30% of children in U.S. day-care centers are carriers. Disease usually manifests as greasy stools alternating between a watery diarrhea, loose stools, and constipation. However, some patients will experience explosive diarrhea. Diagnosis usually comes from microscopically observing the cysts or trophozoite forms of the protozoan in feces. Metronidazole is a drug often used to cure the disease. To prevent it in the first place, proper treatment of community water supplies is essential.

Hepatitis Viruses Target the Liver

The liver is also considered part of the gastrointestinal system, because it provides bile to the intestine and processes the nutrients absorbed from the intestine. Hepatitis is a general term meaning "inflammation of the liver." Although many pathogens can affect this organ, we focus on the major infectious cause, an eclectic group of viruses collectively called the hepatitis viruses. They include a single-stranded, negative-sense RNA virus (hepatitis A, HAV), a double-stranded DNA virus (hepatitis B, HBV), and a single-stranded, positive-sense RNA virus (hepatitis C, HCV). Space does not permit coverage of HDV or HEV.

Table 26.3 compares general features of these viruses. The disease symptoms of infectious hepatitis, regardless of viral cause, include abdominal pain, fever, vomiting, and often dark urine, clay-colored stools, and jaundice. Liver damage from hepatitis is marked by the detection of liver transaminases in serum and an enlarged liver (hepatomegaly).

TABLE 26.3 Comparative Features of Hepatitis Viruses and Disease

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Type	ssRNA, negative sense	DNA, enveloped	ssRNA, positive	ssRNA, negative sense,	ssRNA, positive sense, nonenveloped

TABLE 26.3	Comparative Features of Hepatitis Viruses and Disease				
			sense, enveloped	circular, enveloped	
Incubation period	30 days	90 days	40 days	30 days; requires coinfection with HBV	50 days
Route	Fecal-oral	Parenteral, sexual, perinatal	Parenteral, sexual	Parenteral, sexual	Fecal-oral
Viremia	Transient	Persistent	Persistent	Uncommon	Transient
Severity	Mild	Severe	Mild	Mild to severe	Mild
Chronic	None	90% children 10% adults	50%–60%	80%–90%	None

Hepatitis A virus (HAV) is a single-stranded RNA picornavirus that causes an acute infection spread person to person by the fecal-oral route, but hepatitis A can also be contracted by eating undercooked shellfish collected from contaminated waters. The virus replicates in the intestinal endothelium and is disseminated via the bloodstream to the liver. After replicating in hepatocytes, the progeny enter the bile and are released into the small intestine, explaining why stools are so infectious. Though the virus has an early viremic stage after leaving the intestine, it is rarely transmitted by transfusion, because the viremic stage is transient and ends after liver symptoms develop. In contrast, hepatitis B and C viruses produce persistent viremia and are readily transmitted by transfusion.

Many people who are infected with HAV are asymptomatic or exhibit very mild symptoms that include nausea, vomiting, diarrhea, low-grade fever, and fatigue. As the virus attacks the liver, liver transaminases are detected in serum, patients may become jaundiced (from the accumulation of bilirubin in the skin), and their urine will turn dark brown. Diagnosis can be confirmed by PCR or the detection of IgM antibody to HAV antigens. There is no specific treatment, but the disease usually lasts for only a few months and then resolves without establishing a carrier state. Disease can be prevented, however, by a vaccine containing inactivated virus (called HepA vaccine). The vaccine should be administered starting at 1 year of age. For those not vaccinated, frequent handwashing is important for preventing spread of the disease because it interrupts the fecal-oral cycle.

In contrast to HAV, hepatitis B virus (HBV) is a partially double-stranded circular DNA virus (family *Hepadnaviridae*) that causes diseases of varying severity. These include acute and chronic hepatitis, cirrhosis, and hepatocarcinoma. The virus is also wrapped in a membrane envelope when progeny viruses are released from infected cells. The virion coat protein, a surface antigen, is called HBsAg. The virus makes an excess amount of HBsAg, so it is sometimes extended as a tubular tail on one side of the virus particle and is often found in the blood of infected individuals in the form of noninfectious filamentous and spherical particles (**Fig. 26.21**). The presence of HBsAg in blood is an indicator of HBV infection. There are also nucleic acid and serological tests for HBV RNA and antibodies, respectively.

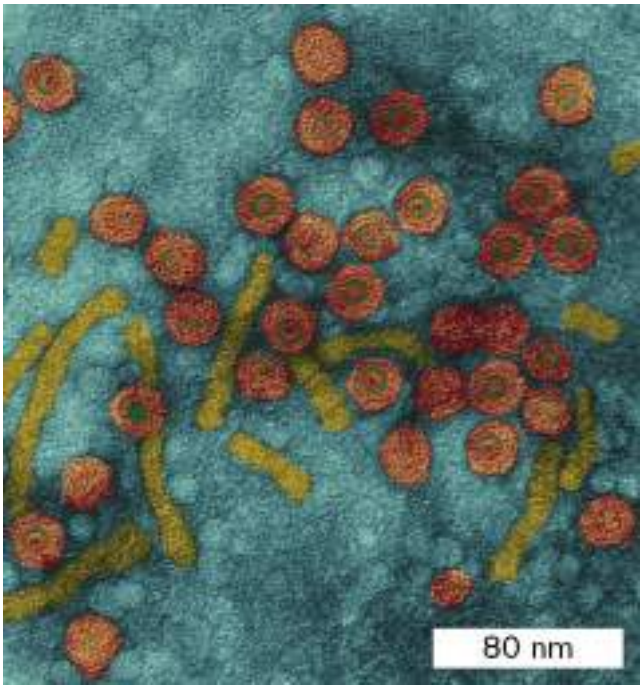


FIGURE 26.21 ■ Structure of hepatitis B virus. Hepatitis B is an enveloped, double-stranded DNA virus in the *Hepadnaviridae* family (TEM). Also shown are the tubular structures made from HepB surface antigen (HBsAg).
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HBV is transferred primarily via parenteral routes such as blood transfusions, contaminated needles shared by IV drug users, and any human body fluid, including saliva, semen, sweat, breast milk, tears, urine, and feces. It can even be transferred transplacentally to a fetus and can be sexually transmitted. Infection by HBV has two stages: a short-term acute phase and a long-term chronic phase that, if it extends beyond 6 months, may never resolve (chronic infection). Symptoms resemble those of the flu but with jaundice and brown urine.

Liver damage caused by HBV infection is due in large part to an efficient cell-mediated immune response. Cytotoxic T cells and natural killer cells cause immune lysis of infected liver cells. Over the long term, chronic hepatitis will lead to a scarred and hardened liver (cirrhosis), the only recourse being a liver transplant. Fortunately, about 90% of people infected are able to fight off infection and never proceed to the chronic stage. A HepB vaccine (made from recombinant HBsAg) is available. Its administration is recommended after birth, followed by booster shots administered by 2 months and 18 months of age. There are also several antiviral agents used to treat acute and chronic HBV disease. One is tenofovir, an inhibitor of HBV reverse transcriptase. Even though HBV is a DNA virus, it replicates using reverse transcription of an RNA intermediate.

Hepatitis C virus (HCV) causes another form of hepatitis. HCV is a single-stranded, positive-sense, linear RNA virus with a lipid coat and is a member of the *Flaviviridae* family. It is transmitted by blood transfusions and causes 90% of transfusion-related cases of hepatitis. It can also be transmitted by needle sticks, razor blades, tattooing, and less frequently by sex. Over 100 million people worldwide are infected with HCV. Screening for HCV (serology or PCR) is recommended for anyone who exhibits signs of hepatitis or practices the risky behaviors noted here. In addition, the CDC recommends that anyone born between 1945 and 1965 (baby boomers) be tested because, for unknown reasons, baby boomers are five times more likely to be infected than other adults.

Most HCV-infected individuals (80%) do not exhibit symptoms, and in those who do, symptoms may not appear for 10–20 years. At least 75% of patients who exhibit symptoms ultimately progress to chronic hepatitis requiring a liver transplant or possibly to liver cancer. Fortunately, infection can be detected using ELISA. Liver biopsies of HCV patients are used to determine the extent of liver damage, which in turn helps establish the stage of disease.

Prevention of HBV or HCV infection for health care personnel includes avoiding inadvertent needle sticks. If such a stick should occur with HBV, anti-HBV immunoglobulin should be administered within 7 days. Currently, no effective post-exposure prophylaxis is recognized for HCV. Chronic hepatitis can be treated with an antiviral protease inhibitor (glecaprevir), which prevents the proteolytic processing of an important HCV polyprotein, and Harvoni, a combination of an RNA chain terminator with an inhibitor of a virus phosphoprotein needed for replication. Though vaccines have been developed for HAV and HBV (see Table 24.5), no vaccine is yet available for HCV.

Note: Because hepatitis viruses can be spread via contaminated blood products, all blood donations collected by the Red Cross and other agencies are tested for the presence of these viruses, as well as for HIV. Thus, the blood supply is safe.

We have examined in this section only a handful of the bacterial, viral, and protozoan microbes that cause gastrointestinal infection. Others are listed in Table 26.4 , and some of the protozoan pathogens are described in Chapter 20 .

TABLE 26.4 Selected Microbes That Cause Diseases of the Gastrointestinal Tract

Etiological agent [a]	Disease	Symptoms	Virulence factors	Source(s)	Treatm
Bacterial					
Campylobacter jejuni (G−)	Gastroenteritis	Fever, muscle pain, watery diarrhea, blood in stool, headache	Cytotoxin, enterotoxin, adhesin	Poultry, unpasteurized milk	Erythror
Clostridioides difficile (G+)	Pseudomembranous enterocolitis	Fever, abdominal pain, diarrhea,	Cytotoxin, antibiotic resistance	Animals, normal microbiota	Vancom

TABLE 26.4	Selected Microbes That Cause Diseases of the Gastrointestinal Tract				
		pseudomembrane in colon			
Clostridium botulinum (G+, anaerobe)	Botulism	Fast onset of symptoms; flaccid paralysis	Neurotoxin	Preformed toxin in foods	Antiseru
Clostridium perfringens (G+)	Gastroenteritis	Watery diarrhea, nausea	Alpha toxin	Soil, food	Self-limi
Enterohemorrhagic *E. coli (G –)*	Gastroenteritis	Bloody diarrhea, HUS	Intimin, Tir, type III secretion, Shiga toxin	Contaminated foods (hamburger) and crops	Oral rehydra antibiot severe
Enterotoxigenic *E. coli (G –)*	Traveler's diarrhea	Watery diarrhea	Labile and stable toxins	Humans; food, water	Oral rehydra
Helicobacter pylori (G–)	Gastric ulcers	Abdominal pain, bleeding, heartburn	Adhesin, urease, CagA, vacuolating toxin	?	Triple dı protocol (omepra clarithrc metroni
Salmonella enterica (G–)	Salmonellosis	Symptoms after 18 h; abdominal pain, diarrhea; invade intestinal M cells	Type III secretion, intracellular growth	Chickens, other animals; fecal-oral route	Oral rehydra antibiot severe
Salmonella enterica serovar Typhi (G–)	Typhoid fever	Headache, fever, chills, abdominal pain, rash (rose spots), hypotension,	Type III secretion, intracellular growth, PhoPQ regulators,	Human carriers (gallbladder reservoir); food, water	Quinolo

TABLE 26.4	Selected Microbes That Cause Diseases of the Gastrointestinal Tract				
		diarrhea in late stages	Vi antigen capsule		
Shigella spp. (G−)	Shigellosis	Bloody diarrhea, HUS	Shiga toxin, type III secretion, intracellular growth, actin-based motility, escape phagosome	Humans; fecal-oral route	Oral rehydra antibiot severe
Staphylococcus aureus (G+)	Staphylococcal food poisoning	Symptoms within 4 h of ingestion; nausea, vomiting, diarrhea	Enterotoxin	Preformed toxin in foods	Support
Vibrio cholerae (G−)	Cholera	Watery diarrhea	Cholera toxin, toxin-coregulated pili (TCPs), ToxR regulator	Human waste–contaminated water	Oral rehydra antibiot
Vibrio parahaemolyticus (G−)	Gastroenteritis	Diarrhea, blood in stool	Enterotoxin	Raw seafood	Self-limi
Viral					
Norovirus (Norwalk virus)	Stomach "flu"	Nausea, vomiting, diarrhea	VP1	Fecal-oral route	Oral rehydra
Rotavirus (most common cause)	Stomach "flu"	Nausea, vomiting,	NSP4	Fecal-oral route	Oral rehydra

TABLE 26.4	Selected Microbes That Cause Diseases of the Gastrointestinal Tract				
		diarrhea			

To Summarize

- **Diarrhea leads to dehydration** , for which fluid replacement is a critical treatment. Antibiotic treatment is usually not recommended.
- **Staphylococcal food poisoning** is not an infection. It is a toxigenic disease.
- **Antibiotic treatments can sometimes cause gastrointestinal disease** (for example, pseudomembranous enterocolitis by *Clostridioides difficile*).
- **The presence of red and white blood cells in fecal contents** is an indication of invasive bacterial infection by intracellular pathogens such as *Shigella* , *Salmonella* , and EIEC.
- **Bacteria that do not invade intestinal cells** usually produce watery diarrhea. EHEC is an exception; the attachment and effacing lesions it produces result in bloody stools.
- **Bacterial toxins** produced by bacterial enteric pathogens can cause systemic symptoms.
- **Rotavirus** is still the single greatest cause of diarrhea worldwide. Increasing use of rotavirus vaccine may eventually leave norovirus as the world's leading cause of diarrhea.
- **The bacterium *Helicobacter pylori*** , a common cause of gastric ulcers, is highly acid resistant and lives in the stomach of half the world's population. It is also a cause of gastric cancer.
- ***Giardia duodenalis* and *Cryptosporidium parvum*** are major protozoan causes of diarrhea worldwide.
- **Hepatitis** is caused by several unrelated viruses; among them, HAV, HBV, and HCV account for most disease. **HAV** is transmitted by the fecal-oral route and does not establish chronic infection. **HBV** and **HCV** can be transmitted by blood products (such as transfusions) and shared hypodermic needles and can lead to chronic hepatitis. Vaccines for HAV and HBV, but not HCV, are available.

Glossary

rehydration therapy
: A medical treatment for dehydration, in which a liquid solution of salts and glucose is delivered orally. Also called **oral rehydration therapy (ORT)** .

rotavirus
: One of a group of nonenveloped dsRNA viruses that cause severe diarrhea in children.

norovirus
: Also known as *Norwalk virus* . A nonenveloped ssRNA virus that causes severe diarrhea in children and adults.

hepatitis
: An inflammation of the liver, caused by infection or by exposure to a toxic substance.

hepatitis A virus (HAV)
: A single-stranded RNA picornavirus that causes an acute infection of the liver spread person-to-person by the fecal-oral route.

hepatitis B virus (HBV)
: A partially double-stranded, circular-DNA hepadnavirus that causes diseases of the liver of varying severity, including acute and chronic hepatitis, cirrhosis, and hepatocarcinoma.

hepatitis C virus (HCV)
: A single-stranded, positive-sense, linear-RNA flavivirus that is transmitted by blood transfusions and causes 90% of transfusion-related cases of hepatitis.

Fig. 23.11D

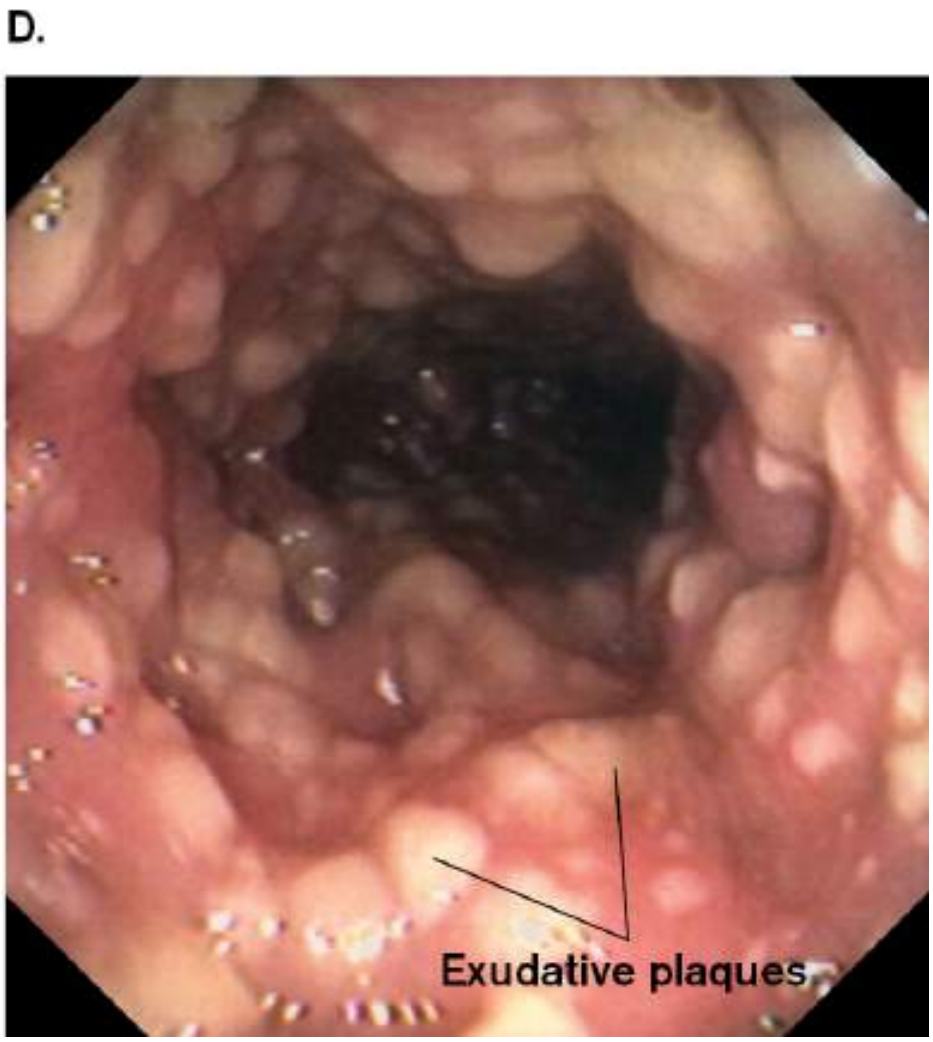


FIGURE 23.11 ■ Potential negative effects of intestinal dysbiosis. D. The firmicute *Clostridioides difficile* is often a minor component of the normal gut microbiome whose numbers are limited by competing gut microbiota. However, antibiotic treatment can kill off the competing microbes, leaving the antibiotic-resistant *C. difficile* to grow unabated. Toxins made by *C. difficile* will kill host cells, causing small exudative plaques to form on the intestinal wall. Plaques coalesce to form a large, bloody, and painful pseudomembrane.

Endnotes

1. Note a: G+ = Gram-positive; G− = Gram-negative. Return to reference a

26.4 Genitourinary Tract Infections

The genital and urinary tracts are certainly different organ systems. One is used for procreation, whereas the other filters and excretes waste products from blood. However, their close association in the body makes it useful to discuss their infections in the same section. Despite being close neighbors, there are two interesting peculiarities to note about the agents that infect these organs: First, viruses and bacteria can infect the genital tract, but viruses rarely cause urinary tract infections. Second, very few pathogens can infect both organ systems.

Urinary Tract Infections

The urinary tract includes the kidneys, ureters, urinary bladder, and urethra. Infections anywhere along this route are called urinary tract infections (UTIs). **Figure 26.22** shows an SEM of a bladder chronically infected with uropathogenic *Escherichia coli* . UTIs are the second most common type of bacterial infection in humans, ranking in frequency just behind respiratory infections such as bronchitis or pneumonia. In the United States, bladder infections and other UTIs result in over 8 million patient visits annually, mostly by women. Estimates are that at least 60% of women will experience a UTI during their lifetime, and 20%–40% of those develop recurrent infections. UTIs result in 100,000 hospital admissions in the United States and over $1 billion in medical expenses each year.



FIGURE 26.22 ■ Urinary tract infection. Bladder cells (blue) with adherent uropathogenic *E. coli* (SEM). White blood cells (yellow) reach out with extracellular traps to immobilize and kill the pathogen.

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Urine, as produced in the kidneys, is normally sterile and was thought to be sterile when stored in the bladder. Studies now show that the bladder has a normal microbiome, although its role in human health is unclear. Why didn't we notice this earlier? All known bacterial causes of urinary tract infections are facultative anaerobes that grow under aerobic conditions. The microbiota of our urinary bladder are typically slow growing and/or anaerobes and do not grow when urine is plated aerobically on blood agar for 24–48 hours, which is the normal procedure used to identify urinary tract pathogens. The current thought is that bladder microbiota are not pathogenic, so the fact that they do not grow under conditions used to identify uropathogens is convenient for the clinical laboratory seeking pathogens.

Bacteria that cause UTIs are introduced into the bladder or kidney in one of four ways:

- **Infection from the urethra to the bladder.** This is the most common route for bladder infections (called cystitis). Bacteria residing along the urethra can ascend to the bladder. This is a more common occurrence in women than in men. Uropathogenic bacteria colonizing the urethra can also be introduced into the bladder by means of mechanical devices such as catheters or cystoscopes that are passed through the urethra into the bladder.
- **Deposition of bacteria from the bloodstream to the kidney.** Kidney infections (called pyelonephritis) can arise when microorganisms from infections elsewhere in the body disseminate via the bloodstream and arrive at the kidney.
- **Descending infection from the kidney to the bladder.** Descending infection occurs when bacteria from an infected kidney are shed into the ureters. The microbes are then carried by urine into the bladder.
- **Ascending infection to the kidney.** In ascending infection, bacteria from an established infection in the bladder ascend along the ureter to infect the kidney. This is the most common route for pyelonephritis.

Thought Question

26.6 Why do you think most urinary tract infections occur in women?

Urine is bacteriostatic to most of the commensal organisms inhabiting the perineum and vagina, such as *Lactobacillus* , *Corynebacterium* , diphtheroids, and *Staphylococcus epidermidis* . In contrast, many Gram-negative organisms thrive in urine. As a result, most urinary tract infections are caused by facultative Gram-negative rods from the GI tract. The most common etiological agents of UTIs are:

- Certain serotypes of *E. coli* that comprise the uropathogenic *E. coli* (75% of all UTIs)
- *Klebsiella* , *Proteus* , *Pseudomonas aeruginosa* , *Enterobacter* (20%)
- *Staphylococcus aureus* , *Enterococcus* , *Chlamydia* , fungi, *Staphylococcus saprophyticus* , other (5%)

Case History: Classic Urinary Tract Infection

Lashandra was 24 years old and had been experiencing back pain, increased frequency of urination, and dysuria (painful or burning urination) over the previous 3 days. This was the first

time Lashandra had ever suffered from persisting dysuria. She consulted her general practitioner, who requested a midstream specimen of urine. Upon microscopic examination, the urine was found to contain more than 50 leukocytes per microliter (normal is fewer than 5) and 35 red blood cells per microliter (normal is 3–20). No epithelial squamous cells (skin cells) were seen, indicating a well-collected midstream catch. The urine culture plated on agar medium yielded more than 10^5 colonies per milliliter of urine of a facultative anaerobic Gram-negative bacillus capable of fermenting lactose.

The first question to ask in this case is whether the patient had a significant UTI. The purpose of the midstream urine collection is to provide laboratory data to make this determination. Even though urine in the bladder is normally considered sterile (see the preceding discussion), urine becomes contaminated with normal skin or GI microbiota that may adhere to the urethral wall. In a midstream collection, the patient urinates briefly, stops to position a collection jar, and resumes urinating to collect the sample. This procedure washes away organisms clinging to the urethra before actually collecting the sample. Nevertheless, the collected sample will still contain low numbers of organisms representing normal microbiota of the urethra. (see Section 28.1 for more on urine collection.)

The number of bacteria per milliliter of urine does not have to reach 10^5, as happened in the case history, to diagnose cystitis. A diagnosis of cystitis can be made in a symptomatic patient when the number of bacteria (single colony type) in a sample is at least 1,000 per milliliter. In fact, relying only on the number of bacteria in urine can be misleading. Some people (especially the elderly) can be asymptomatic yet have bacterial counts of 10^5 per milliliter. These patients have asymptomatic bacteriuria and are not usually treated with antibiotics, unless they are pregnant women. The patient in the case history was symptomatic and had more than enough bacteria in her urine to indicate a UTI.

The laboratory found the organism to be a Gram-negative bacillus that ferments lactose, suggesting *E. coli* as the likely culprit. *E. coli* that can colonize the intestine and infect the urinary tract are called uropathogenic *E. coli* (UPEC). Given that this was the first UTI suffered by the patient, the infection was likely the result of an inadvertent introduction of the gut microbe into the urethra. The organism makes its way up the urethra and into the bladder. As noted earlier, another way the bladder can become infected is via a descending route from the kidney.

Gram-negative rods not only thrive in urine but are also equipped with specialized pili whose terminal receptors bind to the glycolipids and glycoproteins present on urinary tract epithelial cells (**Fig. 26.22**). UPEC strains of *E. coli* , for example, typically have type I pili whose tips attach to mannose receptors on bladder epithelial cells, and P-type pili whose terminal receptor binds to P antigens present more on kidney cells than on bladder cells. P antigen is a so-called blood group marker expressed by approximately 75% of the population. Individuals with P antigen are particularly susceptible to pyelonephritis.

Some patients, predominantly women, suffer with recurrent bladder infections. These infections are thought to be caused in two ways: by a UPEC strain colonizing the intestine that is accidentally reintroduced into the bladder or by UPEC already present in the bladder invading urinary tract epithelial cells to form compact intracellular biofilms, called uropods. (The chapter-opening image shows a tiny, laboratory-made bladder organoid used to examine how *E. coli* forms uropods.) *E. coli* can emerge from these uropods to "reignite" a UTI. What triggers the emergence? Amanda Lewis's laboratory (Washington University School of Medicine in St. Louis; **Fig. 26.23**), using a mouse model, found that exposing the bladder to *Gardnerella vaginalis* , a Gram-positive bacillus that is part of the vaginal microbiome, can trigger the egress of *E. coli* from a uropod. Lewis has proposed a new paradigm, called "covert pathogenesis," in which transient exposure of a dormant pathogen to some member of the human microbiome can drive the recurrence of disease.



FIGURE 26.23 ■ Amanda Lewis studies recurrent urinary tract infections.
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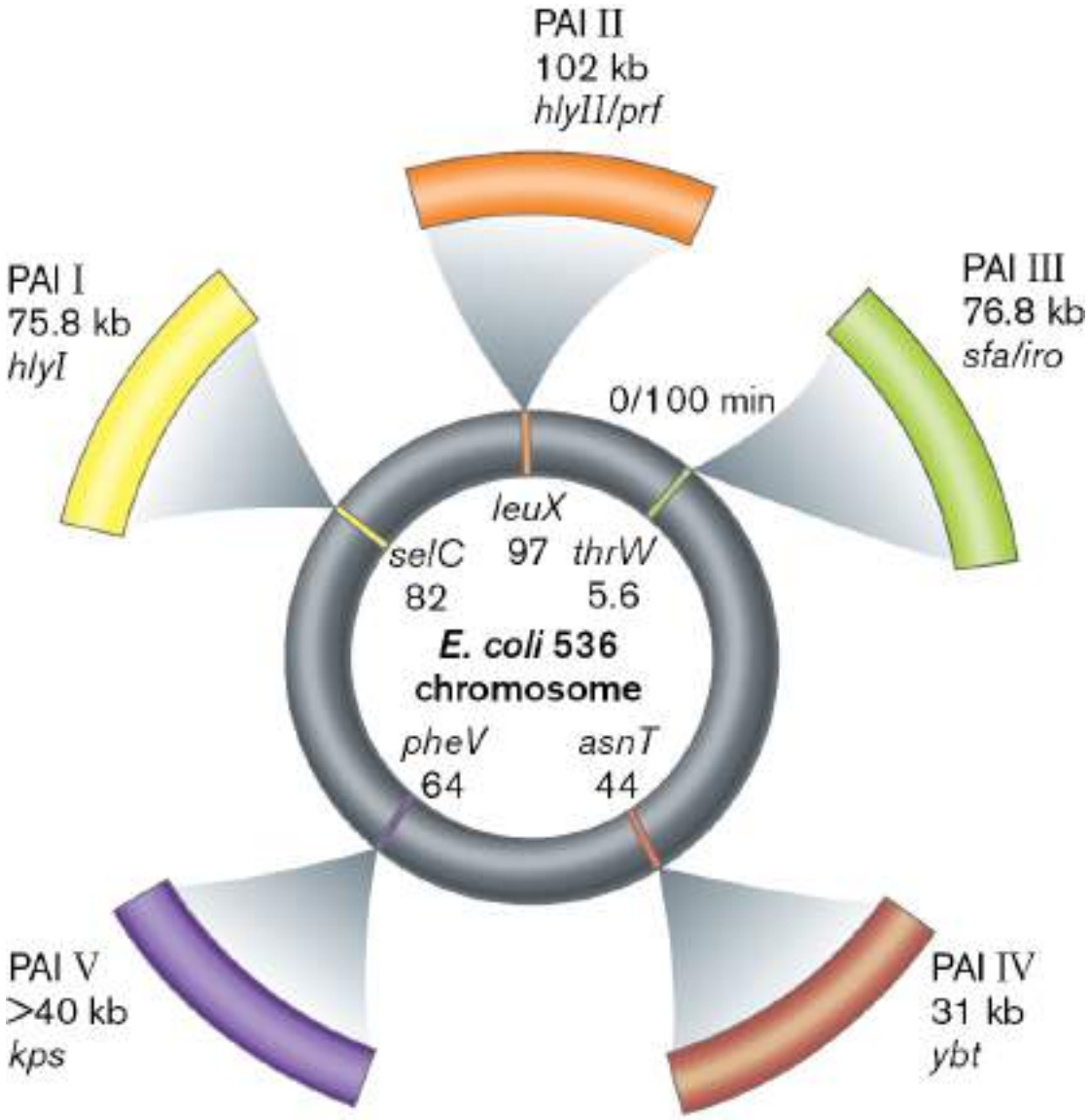


FIGURE 26.24 ■ Uropathogenic *E. coli* . Distribution of pathogenicity islands (PAIs) in uropathogenic *E. coli* . The location of each insert is given in map units within the circle representing the genome. The 0–100 map units are called centisomes. Each centisome is approx. 44 kb of DNA. Zero is arbitrarily placed at the *thr* (threonine) gene. The origin of replication on this map is near 82 centisomes. A chromosomal gene flanking the insert is also provided. The size of each island is shown above the insert. A key virulence gene for each island is listed.

Urinary tract infections are frequently acquired during a hospital stay (also called nosocomial, or hospital-acquired, infections). These infections are often precipitated by urinary catheters. In these cases, the causal organism is less likely to be *E. coli* and more likely to be another Gram-negative bacterium or *Staphylococcus* . Many UTIs resolve spontaneously, but others can progress to pyelonephritis (destroying the kidney) or septicemia. As a result, antibiotic therapy is recommended. In older patients, UTIs frequently show atypical symptoms, including delirium, which disappears when the UTI is treated.

How can recurrent UTIs be managed? One way would be to prevent UPEC strains from colonizing the intestine. A number of laboratories have found that d-mannose or a mannoside will block type I pili on UPEC from binding to host cell mannose receptors and prevent UPEC strains from colonizing the intestine and the bladder. The idea, still not tested, is that simultaneously treating a patient with antibiotics to clear the UTI, along with the mannoside to prevent UPEC from colonizing the intestine or recolonizing the bladder, will reduce the number of recurrent UTIs.

Thought Question

26.7 Urine samples collected from six hospital patients were placed on a table at the nurses' station awaiting pickup from the microbiology lab. Several hours later, a courier retrieved the samples and transported them to the lab. The next day, the lab reported that four of the six patients had UTIs. Would you consider these results reliable? Would you start treatment based on these results?

What makes uropathogenic *E. coli* different from other strains of *E. coli* ? This is a question still under investigation, but genomic analysis has exposed five pathogenicity islands unique to these strains (**Fig. 26.24**). The functions of these pathogenicity islands are still under investigation.

Sexually Transmitted Infections

Sexually transmitted infections (STIs) are defined as infections transmitted primarily through sexual contact. The organisms or viruses involved are generally very susceptible to drying and require direct physical contact with mucous membranes for transmission. Because sex can take many forms in addition to intercourse, these microbes can initiate disease in the urogenital tract, rectum, or oral cavities. Condoms can prevent transmission but do so, of course, only when used properly. Examples of common sexually transmitted infections are listed in Table 26.5 .

TABLE 26.5 Common Sexually Transmitted Infections

Disease	Symptoms	Etiological agent [a]	Virulence factors	Treatment	Reported cases
Gonorrhea	Purulent discharge, burning urination; can lead to sterility	*Neisseria gonorrhoeae* (G−)	Type IV pili, phase variation	Ceftriaxone plus azithromycin	468,514 [b]

TABLE 26.5	**Common Sexually Transmitted Infections**				
Syphilis	1°: chancre; 2°: joint pain, rash; 3°: gummata, aneurism, central nervous system damage	*Treponema pallidum* (spirochete)	Motility	Penicillin	88,042 [b]
Nongonococcal urethritis	Watery or mucoid urethral discharge, burning urination	*Chlamydia trachomatis* (Gram-negative–like)	Intracellular growth; prevents phagolysosome fusion	Azithromycin	1.6 million [b]
Trichomoniasis	Vaginal itching, painful urination, strawberry cervix	*Trichomonas vaginalis* (protozoan)	Cytotoxin	Metronidazole	2.3 million [c]
Chancroid	Painful genital lesion	*Haemophilus ducreyi* (G−)	?	Erythromycin	7 [b]
HIV diagnoses ranging from asymptomatic to AIDS	For AIDS, fever, diarrhea, cough, night sweats, fatigue, opportunistic infections	HIV	gp120, Rev, Nef, and Tat proteins	Azidothymidine (AZT), protease inhibitors, zidovudine	34,775 [b]

TABLE 26.5	Common Sexually Transmitted Infections				
Genital herpes	Painful ulcer on external genitals, painful urination	Herpes simplex 2	Cell fusion protein, complement-binding protein, latency	Acyclovir, iododeoxyuridine	50 million [c]
Genital warts	Warts on external genitals	Human papillomavirus	E6, E7 proteins	Vaccine now available	50 million [c]

Note: Because not all infections progress to diseases, the term "sexually transmitted infection" (STI) is preferred over the older phrase "sexually transmitted disease" (STD).

An important part of limiting the spread of any STI is to identify and treat all sexual partners the patient has had in the previous 60 days. Either the patient (preferably) or the health care provider can notify the affected people. In some instances, patients can be supplied with medication to give directly to their partners. STIs are also reportable to state and federal health agencies, such as the Centers for Disease Control and Prevention.

Case History: Secondary Syphilis

An 18-year-old pregnant woman came to the county urgent-care clinic with a low-grade fever, malaise, and headache. She was sent home with a diagnosis of influenza. She again sought treatment 7 days later, after she discovered a macular rash (flat, red) developing on her trunk, arms, palms of her hands, and soles of her feet. When asked, the patient revealed that 1 year earlier, she had had a painless ulcer on her vagina that healed spontaneously. She was diagnosed with secondary syphilis—a diagnosis confirmed by a serological test. She was given a single intramuscular injection of penicillin and told that her sexual partners had to be treated as well.

The vaginal ulcer, the long latent period, and the secondary development of a rash on the hands and feet described in the case history are classic symptoms of syphilis. Christopher Columbus and/or his crew are thought to have inadvertently delivered the treponeme that causes syphilis from the Americas to Europe in the fifteenth century, but syphilis as a disease was not recognized until the sixteenth century. The infectious agent, a spirochete named *Treponema pallidum* , was finally discovered in 1905 (**Fig. 26.25A**). (Chapter 18 describes spirochete structure.) But another 113 years would pass before this anaerobe would be cultured in vitro. Steven Norris (University of Texas Health Science Center at Houston) finally achieved long-term logarithmic

growth of *T. pallidum* in 2018, by periodically subculturing (6–7 days) and feeding the treponeme in a microaerobic rabbit epithelial cell coincubation system.



FIGURE 26.25 ■ Syphilis. A. *Treponema pallidum* (dark-field microscopy). Organisms are 10–25 μm long. **B.** Chancre of primary syphilis. **C.** Rash of secondary syphilis.

CDC SUSAN LINDSAY
CDC/M. REIN, VD
CDC/M. REIN, VD

The disease syphilis has several stages. The incubation stage can last from 2 to 6 weeks after transmission, during which time the organism multiplies and spreads throughout the body. Primary syphilis is defined by an inflammatory reaction at the site of infection called a chancre (**Fig. 26.25B**). About a centimeter in diameter, the chancre is painless and hard, and it contains spirochetes. Patients are often too embarrassed to seek medical attention and, because it is painless, hope it will just go away. It does go away after several weeks and without scarring. The disease has now entered the primary latent stage. Over the next 5 years, symptoms may be absent, but at any time, as described in the case history, the infected person can develop the rash typical of secondary syphilis (**Fig. 26.25C**).

The rash of secondary syphilis can be similar to rashes produced by many different diseases, which contributes to syphilis's nickname as the "great imitator." In this stage the patient remains contagious. The symptoms eventually resolve, and the patient reenters a latent phase of syphilis. Some patients eventually progress over years to tertiary syphilis and develop many cardiovascular and neurological symptoms. Neurological symptoms resulting from syphilis at any stage of the disease are referred to as neurosyphilis. The patient can develop dementia and eventually die from the disease.

The presence of *T. pallidum* in tissues can be detected with fluorescent antibody, but the initial screen is usually serological (that is, patient serum is tested for antibodies). Antibiotics (penicillin or doxycycline) are useful for eradicating the organism, but there is no vaccine, and cure does not confer immunity.

The disease is particularly dangerous in pregnant women. The treponeme can cross the placental barrier and infect the fetus to cause congenital syphilis . At birth, infected newborns will have notched teeth (visible on X-rays), perforated palates, and other congenital defects. Women should be screened for syphilis as part of their prenatal testing to prevent these congenital infections. Nevertheless, cases of congenital syphilis have increased nearly threefold since 2015.

Crossing the placental barrier. Several viral and bacterial pathogens can, like *Treponema pallidum* , cross the placental barrier. Known as the TORCH complex, these pathogens include *T oxoplasma* , r ubella virus (German measles), c ytomegalovirus (CMV), and h erpes simplex 2. The "O" stands for "others," such as *T. pallidum* , *Listeria monocytogenes* , HIV, and varicella-zoster. Bacteria that cross the barrier do so in one of two ways. They may move from the mother's blood

across the placental villus using intracellular cell-to-cell spread to reach and breach fetal capillaries. Alternatively, the pathogen can initiate an acute inflammatory response that disrupts the integrity of the placental barrier. In contrast, viral pathogens generally use white blood cells (macrophages or lymphocytes) as cellular "Uber drivers" to carry them across the placenta.

The Tuskegee experiment. Unfortunately, much of what we know about untreated syphilis is the result of the infamous Tuskegee experiment entitled "Untreated Syphilis in the Negro Male" conducted in Alabama in the 1930s. Through dubious means and deception, a group of Black men was enlisted in a study that promised treatment but whose real purpose was to observe how the disease progressed without treatment. Today, such experiments are barred, thanks to strict oversight by institutional review boards (IRBs) that require human subjects to sign informed consent forms. A case study on the Tuskegee experiment can be found on the Internet at the National Science Teaching Association website (search the site for "Bad Blood").

Chlamydial Infections Are Often Silent

Chlamydia is the most frequently reported sexually transmitted infectious disease in the United States (1.8 million cases in 2019), according to the Centers for Disease Control and Prevention, but many people are unaware that they are infected. Three-fourths of infected women, for instance, have no symptoms.

The chlamydias are unusual Gram-negative organisms with a unique developmental cycle. (Chapter 18 describes chlamydial morphology.) They are obligate intracellular pathogens that start as a small, nonreplicating, infectious elementary body that enters target eukaryotic cells. Once inside vacuoles, they begin to enlarge into replicating reticulate bodies (**Fig. 26.26**). As the vacuole fills, the reticulate bodies divide to become new nonreplicating elementary bodies. *Chlamydia trachomatis* causes a sexually transmitted infection called chlamydia but also an eye disease called trachoma, a major worldwide cause of blindness. *Chlamydia* (briefly *Chlamydophila*) *pneumoniae* and *Chlamydia psittaci* are chlamydial species that cause pneumonia but not STIs.

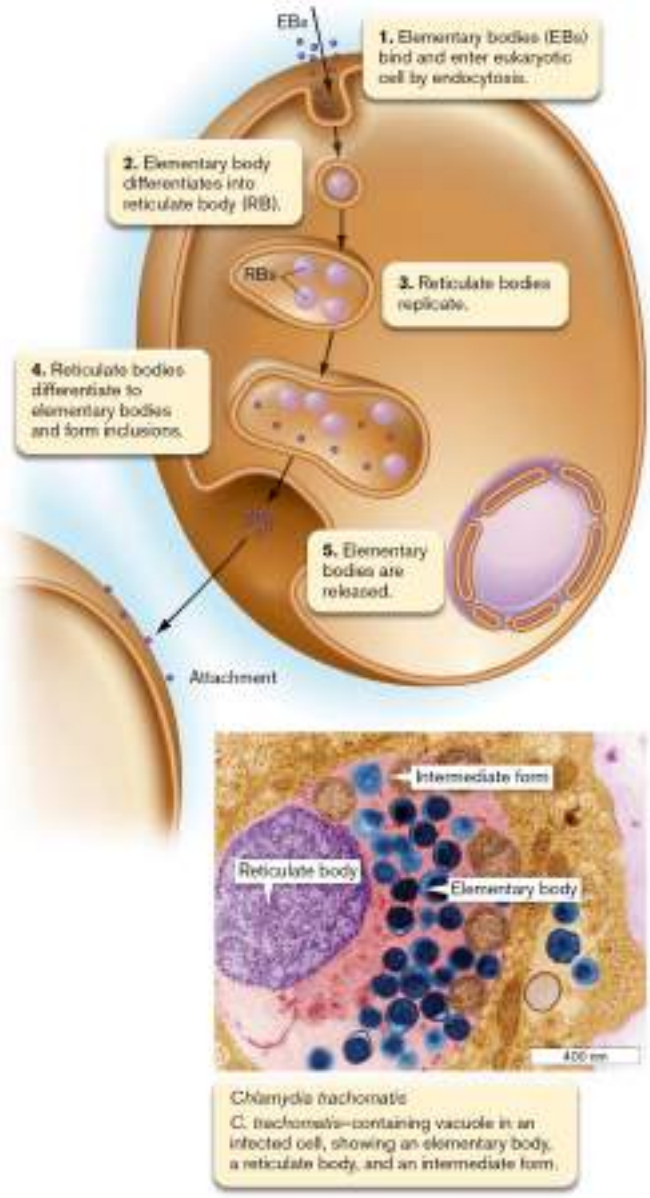


FIGURE 26.26 ■ Replication cycle of *Chlamydia* . Inset: EM of a *C. trachomatis* – containing vacuole in an infected cell, showing a reticulate body, infectious elementary bodies, and intermediate forms.

DR. FRED HOSSLER/VISUALS UNLIMITED, INC.

People most at risk of developing genitourinary tract infections with chlamydia are young, sexually active men and women; anybody who has recently changed sexual partners; and anybody who has recently had another sexually transmitted infection. The astute clinician knows that when one STI is discovered, others may also be present.

Left untreated, chlamydia can cause serious health problems. In female patients, the organism can produce pelvic inflammatory disease, a damaging infection of the uterus and fallopian tubes that can be caused by several different microbial species. The damage produced can lead to infertility, tubal pregnancies, and chronic pelvic pain. Male patients left untreated can suffer urethral and testicular infections and a serious form of arthritis.

Case History: Gonorrhea

A 22-year-old mechanic saw his family doctor for treatment of painful urination and urethral discharge. The patient was sexually active, with three regular and several "one time–good time" partners. Physical examination was unremarkable except for prevalent urethral discharge. The discharge was Gram-stained and sent for culture. The Gram stain revealed many pus cells, some of which contained numerous phagocytosed Gram-negative diplococci (***Fig. 26.27A*** *). Blood was drawn for syphilis serology, which proved negative. The patient was given a single intramuscular injection of ceftriaxone, and oral doxycycline was prescribed for 7 days. The bacteriology lab was able to recover the bacteria seen in the Gram-stained smear of the urethral discharge. The organism produced characteristic colonies on chocolate agar (agar plates containing heat-lysed red blood cells that turn the medium chocolate brown;* ***Fig. 26.27B*** *). The case was subsequently reported to the state public health department. When the patient came back for his return visit, his symptoms had resolved, and a repeat culture was negative.*

The disease here is classic gonorrhea caused by *Neisseria gonorrhoeae* . A characteristic that distinguishes *Neisseria* infections from *Chlamydia* infections is that bacterial cells are microscopically visible in gonorrheal discharges but not in chlamydial discharges, even though they are there (too small to see). Gonorrhea has been a problem for centuries and remains epidemic in this country today (616,392 cases in 2019). Symptoms generally occur 2–7 days after infection, but they can take as long as 30 days to develop. Most infected men (85%–90%) exhibit symptoms that can include painful urination, yellowish white discharge from the penis, and in some cases, swelling of the testicles and penis. The Greek physician Galen (CE 129–ca. 199) originally mistook the discharge for semen. This mistake led to the name *gonorrhea* , which means "flow of seed."

In contrast to men, most infected women (80%) do not exhibit symptoms and constitute the major reservoir of the organism. If they are asymptomatic, they have no reason to seek treatment and can unknowingly spread the disease. When symptoms are present, they are usually mild. Most symptomatic women will experience a painful burning sensation when urinating and will notice vaginal discharge that is yellow or occasionally bloody. They may also complain of cramps or pain in the lower abdomen, sometimes with fever or nausea. As the infection spreads throughout the reproductive organs (uterus and fallopian tubes), pelvic inflammatory disease occurs (see earlier discussion of chlamydia). There is no serological test or vaccine for gonorrhea because the organism frequently changes the structure of its surface antigens in a type of phase variation (see Section 10.5).

Although *N. gonorrhoeae* is generally serum sensitive, owing to its sensitivity to complement (see Section 23.6), certain serum-resistant strains can make their way to the bloodstream and carry infection throughout the body. As a result, both sexes can develop purulent arthritis (joint fluid containing pus), endocarditis, or meningitis. An infected mother can also infect her newborn during parturition (birth), leading to a serious eye infection called ophthalmia neonatorum. Because of this risk and because most infected women are asymptomatic, all newborns receive antimicrobial eyedrops at birth.

Because adults engage in a variety of sexual practices, *N. gonorrhoeae* can also infect the anus or the pharynx, where it can develop into a mild sore throat. These infections generally remain unrecognized until a sex partner presents with a more typical form of genitourinary gonorrhea. Because no lasting immunity is built up, reinfection with *N. gonorrhoeae* is possible. Reinfection occurs, in part, because of phase variation in various surface antigens and because the organism can apparently bind to $CD4^+$ T cells, inhibiting their activation and proliferation to become memory T cells (**Fig. 26.27C**).

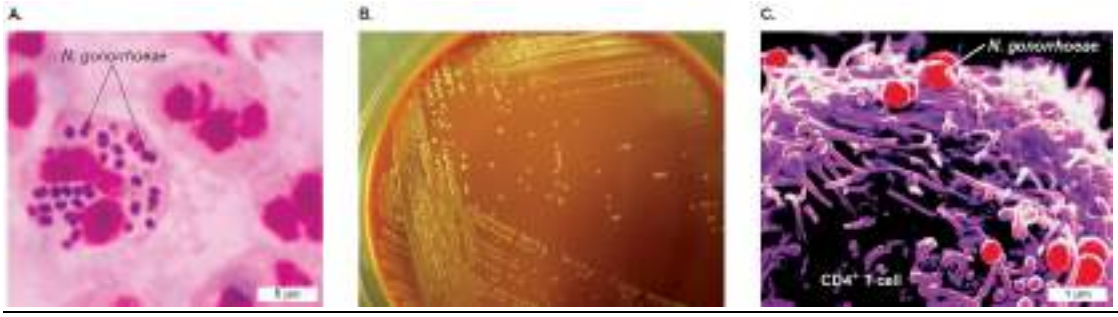


FIGURE 26.27 ■ ***Neisseria gonorrhoeae*** **. A.** Within pus-filled exudates, the Gram-negative diplococci are found intracellularly inside PMNs. The intracellular bacteria in this case are no longer viable, having been killed by the antimicrobial mechanisms of the white cell. **B.** Colonies of *N. gonorrhoeae* growing on chocolate agar. **C.** *N. gonorrhoeae* binding to CD4 $^{+}$ T cells, inhibiting T-cell activation and proliferation, which may explain the ease of reinfection (colorized SEM).

DR. A. M. SIEGELMAN/VISUALS UNLIMITED
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NAT. IMMUNOL. 2002. **3** (3), COVER. PHOTO COURTESY OF DR. IAN C. BOULTON AND DR. GRAY-OWEN.

Over the decades, *N. gonorrhoeae* has incrementally developed resistance to many antibiotics used in its treatment, but there has always been a new, effective drug ready to take the place of the old drug. Soon, this may no longer be the case. To prevent treatment failures, the CDC recommends dual antibiotic therapy that includes an intramuscular injection of ceftriaxone and oral azithromycin or tetracycline. However, the incidence of ceftriaxone-resistant strains of *N. gonorrhoeae* overseas is increasing. The alarm has been raised that we must develop new antibiotics if we are to prevent an uncontrollable explosion of cases of this already epidemic disease.

Thought Question

26.8 Aside from the CDC guidelines for treating gonorrhea, why else do you suppose the patient in this case was treated with doxycycline (a derivative of tetracycline)?

HIV Causes AIDS, a Sexually Transmitted and Blood-Borne Disease

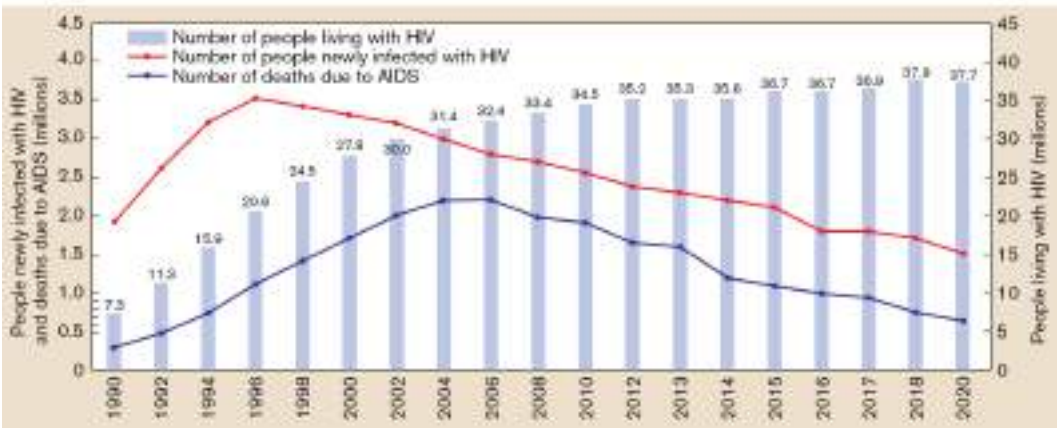
Though HIV (human immunodeficiency virus) is believed to have originated around the year 1900, it was not discovered until 1981, when the virus caused the greatest pandemic of the late twentieth century. HIV remains a serious problem today, especially in Africa, which is home to nearly two-thirds of the people living with HIV worldwide. HIV has claimed the lives of almost 2 million people per year worldwide (about 14,000 per year in the United States). Women make up about 19% of new AIDS cases per year in the United States, the majority resulting from heterosexual sex. The molecular biology and virulence of HIV are discussed in Chapters 11 and 25 . This section focuses on the disease stages of HIV leading up to acquired immunodeficiency syndrome (AIDS), the end-stage HIV disease.

HIV, a lentivirus in the retroviral family, is a prominent example of viruses that can be transmitted either sexually (vaginally, orally, anally—homosexually or heterosexually) or through

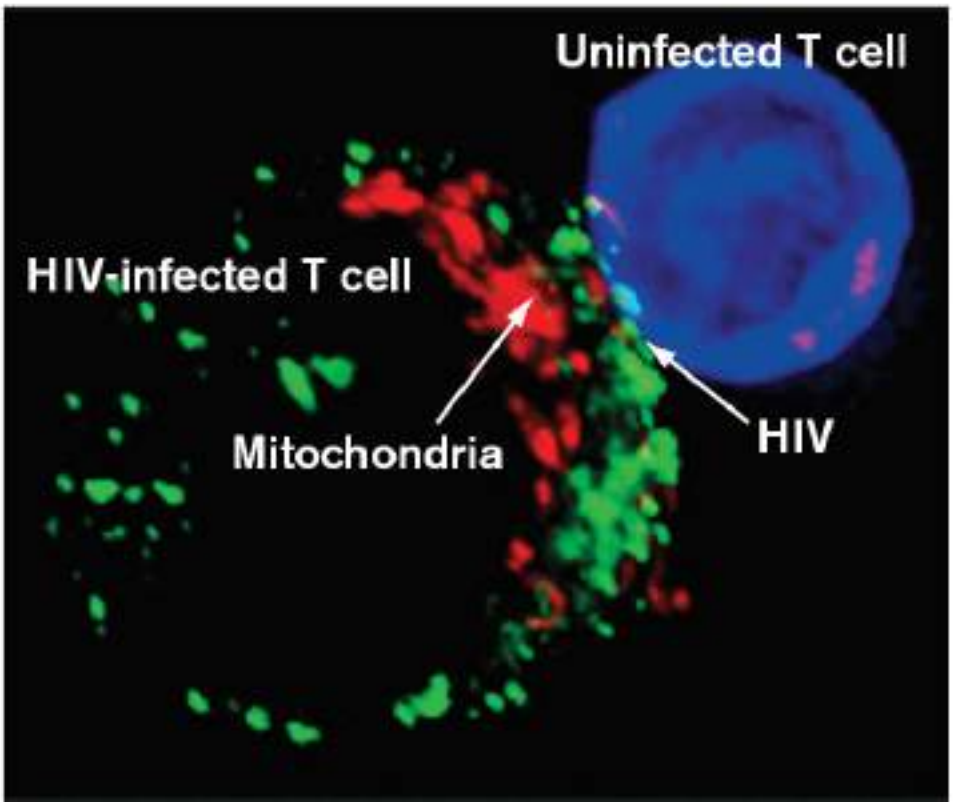
direct contact with body fluids, such as occurs with blood transfusion or the sharing of hypodermic needles by intravenous drug users. HIV is not transmitted by kissing, tears, or mosquito bites. It can, however, be transferred vertically from mother to fetus through the placenta (transplacental transfer). Although the virus disseminates systemically throughout the host, we discuss HIV infections in this section because sexual contact remains the major route of transmission.

Figure 26.28A shows the worldwide decrease in the number of newly infected HIV patients and deaths due to AIDS. The number of people living with HIV has increased, however, because of the development of more effective antiviral treatments.

A.



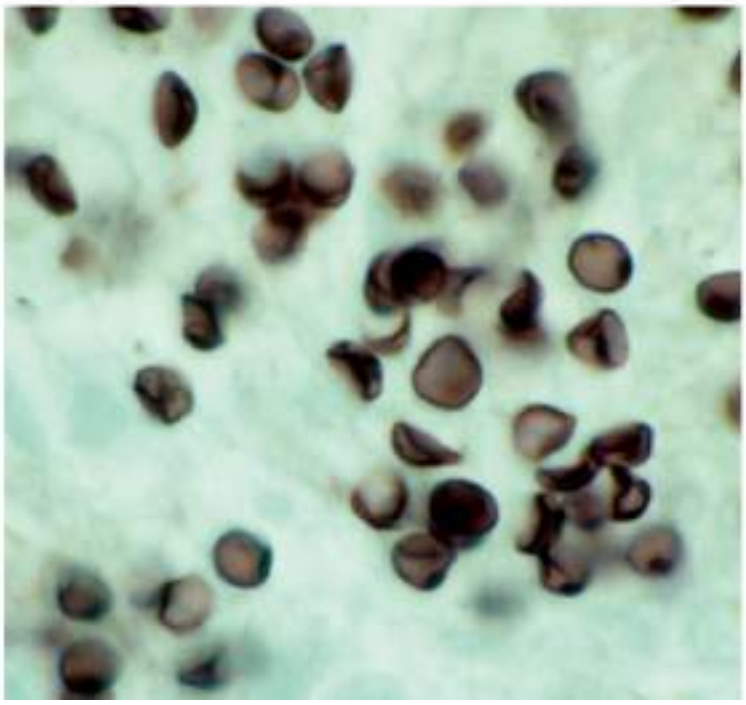
B.



C.



D.



E.



FIGURE 26.28 ■ Acquired immunodeficiency syndrome. A. HIV infections and AIDS deaths worldwide. The number of people living with HIV continues to increase, yet the number of people newly infected with HIV and the number of deaths due to AIDS have decreased. **B.** HIV (green) can directly transfer from an infected to an uninfected T cell by virological synapse. **C.** Oral candidiasis (thrush). The white patches are caused by secondary infection by the yeast *Candida albicans* . **D.** *Pneumocystis jirovecii* infection of the lung. Note the cuplike appearance of the fungus, almost like crushed Ping-Pong balls. Organisms range from 2 to 6 μm in diameter. **E.** Kaposi's sarcoma (oval spots). *Source:* Part A based on data from the World Health Organization.

COVER. IMAGE COURTESY OF E. GROPPELLI ET AL. *J. VIROL.* 2015. **89** : DOI: 10.1128/JVI.02425–14
SRUILK/SHUTTERSTOCK
DR. F. C. SKVARA/VISUALS UNLIMITED
SPL/SCIENCE SOURCE

Once HIV enters the bloodstream, it infects $CD4^+$ T cells and macrophages (which also have CD4 on their surface). The virus replicates very rapidly, producing a billion particles per day, and it can spread directly from cell to cell via virological synapses (**Fig. 26.28B**). When infected and uninfected T cells make contact, HIV virions and mitochondria (to supply energy) line up at the contact interface where transmission occurs. Viral replication starts to kill the $CD4^+$ T cells, which progressively decrease in number.

HIV infection has four stages:

1. A primary stage beginning with seroconversion (finding antibodies to the virus)
2. Clinical latency (slow steady loss of T cells without symptoms or sometimes swollen lymph nodes)
3. Early symptomatic disease (formerly called AIDS-related complex)
4. Acquired immunodeficiency syndrome (AIDS)

Symptoms in the early symptomatic stage can include fever, headache, macular rash, and weight loss. The symptoms can manifest within a few months of infection, resolve within a few weeks, and then recur. As T-cell numbers decline, the debilitated immune system leaves the victim susceptible to secondary infections such as thrush (**Fig. 26.28C**), caused by the yeast *Candida albicans* (candidiasis) and related species.

Monitoring an HIV patient involves assaying blood for viral load using quantitative PCR to detect HIV-specific genes, detecting anti-HIV antibodies, and determining the $CD4^+$ T-cell count. Remember, a person who is HIV-positive does not necessarily have AIDS, which may take years to develop. The CDC defines a patient with AIDS as someone who is HIV-positive with a $CD4^+$ cell count of less than 200 cells per microliter or who has contracted an AIDS indicator disease. For example, once the $CD4^+$ T-cell population falls below 500 cells per microliter, opportunistic infections start to arise. Opportunistic infections include pneumonia by *Mycobacterium avium-intracellulare* or *Pneumocystis jirovecii* (**Fig. 26.28D**), cryptococcal meningitis, *Histoplasma capsulatum* infection, and tuberculosis. The presence of these diseases indicates that the patient has AIDS, regardless of the $CD4^+$ count.

Various cancers are also AIDS indicator diseases. AIDS patients are more susceptible to cancers because their depressed immune systems cannot detect and destroy cancer cells generated by secondary agents. Kaposi's sarcoma (**Fig. 26.28E**), for instance, is a common cancer seen in AIDS patients that is caused by human herpesvirus type 8 (HHV8). Kaposi's sarcoma originates in endothelial or lymphatic cells, but the resulting tumors can develop anywhere—for example, gastrointestinal tract, mouth, lungs, skin, or brain.

More than four decades after the HIV pandemic began, a vaccine for HIV may finally be close at hand. Scientists at the National Institutes of Health (NIH) collaborating with Moderna, one of the first companies to develop an mRNA vaccine for COVID-19, have devised a similar vaccine for HIV that appears to be working. The HIV vaccine carries mRNA encoding two key proteins: Env from HIV and Gag from the closely related simian immunodeficiency virus (SIV). Env protein is normally cleaved by a host protease (furin) into gp120 and gp41, two proteins critical for HIV entry. Gp120 binds to CD4 and the coreceptor CXCR4. The gp41 protein then engineers fusion between the viral and host cell membranes (described in Fig. 11.26). The end result is infection.

SIV Gag mRNA was included in the vaccine because Gag induces muscle cells of the test animals, macaque monkeys, to produce and release virus-like particles (VLPs). The membrane surfaces of these VLPs incorporate multiple Env glycoproteins when Env is coexpressed in the same cell. The Env-Gag VLPs cannot cause disease because they lack the genes to do so, but they can stimulate suitable immune responses. Importantly, the Env gene selected for the vaccine presents epitopes that are immutable—that is, altering any of them in a natural HIV virus would destroy infectivity. Thus, immune responses to these epitopes should prove protective against many variants of HIV.

Even though a vaccine to prevent AIDS is not yet available, progression of the disease can be controlled by antiretroviral drugs that inhibit several critical features of HIV biology: entry, integration, reverse transcription, and the proteolytic processing of viral polyproteins. These treatment regimens (antiretroviral therapy, or ART; see Chapter 27) have made HIV an increasingly survivable infection. Consider this: In the past, nearly all HIV-infected individuals eventually became ill and died from AIDS-related diseases, but in the United States at least half of, if not most, HIV-positive people now die from diseases unrelated to HIV (for example, heart attack). Because HIV infection is now considered a treatable disease, the CDC recommends routine screening for HIV.

Can HIV infection be cured? Well, sort of. Only two people have been effectively "cured" of HIV, by putting the virus in sustained remission. The first was Timothy Ray Brown, who was diagnosed in 2006 with leukemia and HIV. In an attempt to eradicate both diseases, doctors destroyed Brown's white cells with chemotherapy and transplanted bone marrow from a donor who lacked

CCR5, which is the coreceptor needed for HIV to enter T cells. The transplant, performed in 2008, successfully repopulated Brown's blood with HIV-resistant T cells. Mr. Brown has not needed antiretroviral therapy for more than 12 years, even though traces of the HIV genome remain. Unfortunately, this approach repeatedly failed with other patients until 2016 when Adam Castillejo, a patient from London with Hodgkin's lymphoma, received a stem cell transplant from another CCR5-deficient donor. Mr. Castillejo has been HIV-free for over five years without needing antiretroviral therapy.

Because HIV DNA integrates into the genome of an infected cell, it has been impossible to completely cure anyone of the infection. However, a study by Kamel Khalili proved that the CRISPR-Cas9 system described in Chapter 12 can be engineered to "surgically" remove proviral HIV DNA from infected T cells. In 2021, the U.S. Food and Drug Administration gave the startup company Excision BioTherapeutics permission to use an adeno-associated virus and CRISPR technology to excise HIV DNA from infected cells.

Thought Question

26.9 Like the cause of plague, HIV is a blood-borne pathogen. Why, then, do you think fleas and mosquitoes fail to transmit HIV?

The Protozoan *Trichomonas vaginalis* Produces a Common Vaginal Infection

Trichomonas vaginalis is a flagellated protozoan (**Fig. 26.29**) that causes an unpleasant, sexually transmitted vaginal disease called trichomoniasis. Approximately 2–3 million infections occur each year in the United States. Both men and women can be infected; however, men are usually asymptomatic. Even among infected women, 25%–50% are considered asymptomatic carriers.



FIGURE 26.29 ■ *Trichomonas vaginalis* . *T. vaginalis* is a protozoan that causes a common sexually transmitted infection (SEM).
DAVID M. PHILLIPS/VISUALS UNLIMITED

There is no cyst in the life cycle of *T. vaginalis* , so transmission is via the trophozoite stage only (the form of a protozoan in the feeding stage). A female patient with trichomoniasis may complain of vaginal itching and/or burning and a musty vaginal odor. An abnormal vaginal discharge also may be present. A male patient may complain of painful urination (dysuria), urethral or testicular pain, and lower abdominal pain.

Owing to colonization by lactobacilli (which produce large amounts of lactic acid), the normal, healthy vagina usually, but not always, has a pH of less than 4.5. However, since *T. vaginalis* feeds on bacteria, the pH of the vagina rises as the numbers of lactobacilli decrease. Definitive diagnosis requires microscopically identifying the flagellated protozoan in vaginal secretions. PMNs, which

are the primary host defense against the organism, are also usually present. Like giardiasis, this disease is treated with metronidazole.

To Summarize

- **Urinary tract infections (UTIs)** include cystitis (bladder) and pyelonephritis (kidney). ***E. coli*** is the most common cause of UTIs.
- **Cystitis can develop** from bacteria ascending up the urethra (most common route) or descending down a ureter from an infected kidney.
- **Pyelonephritis can develop** from bacteria ascending along a ureter from an infected bladder (most common route) or from bacteria in the bloodstream disseminating from an infection elsewhere in the body.
- **Syphilis, chlamydia, and gonorrhea** are the most common sexually transmitted infections.
- **A patient with one STI** often has another STI too.
- **Complement prevents bloodstream dissemination** of *Neisseria gonorrhoeae* , which lacks a carbohydrate capsule. Because the organism frequently changes the structure of its surface antigens, no vaccine is available for *N. gonorrhoeae* .
- **HIV depletion of CD4 ^{1} T cells** results in lethal secondary infections and cancers.
- ***Trichomonas vaginalis*** is a flagellated protozoan that causes a sexually transmitted vaginal infection. The reservoirs for this organism are the male urethra and female vagina.

Glossary

cystitis
: Bladder infection.

pyelonephritis
: Kidney infection.

primary syphilis
: The initial inflammatory reaction (chancre) at the site of infection by *Treponema pallidum* .

chancre
: A painless, hard lesion due to an inflammatory reaction at the site of infection by *Treponema pallidum* , the causative agent of syphilis.

secondary syphilis
: A rash that may appear at some point after the primary latent stage of syphilis.

tertiary syphilis
: A final stage of syphilis, manifested by cardiovascular and nervous system symptoms.

congenital syphilis
: Syphilis contracted in utero.

chlamydia
: 1. A pathogenic bacterium lacking a cell wall; chlamydias (or chlamydiae) grow within human or animal cells, transmitting as elementary bodies to other cells. 2. A disease caused by chlamydia cells. The most frequently reported sexually transmitted disease in the United States. Symptoms range from none, to a burning sensation upon urination, to sterility.

Fig. 11.26

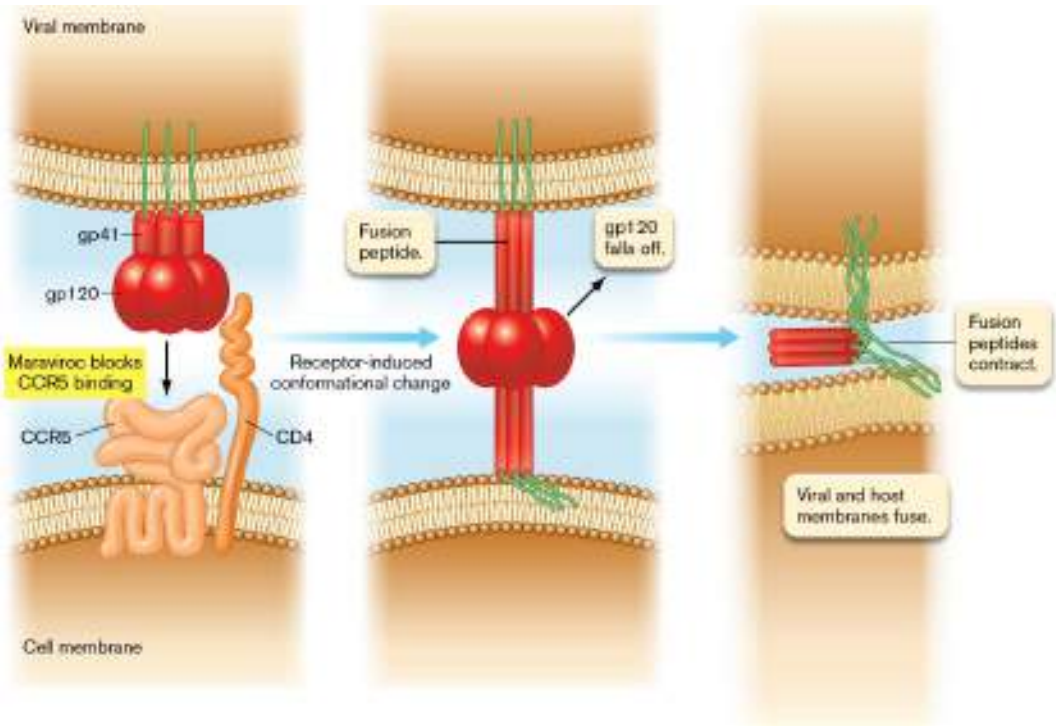


FIGURE 11.26 ■ HIV-1 attachment to host cell. The SU (gp120) subunits of the spike protein complex attach to the receptor (CD4 cell-surface protein) and to CCR5. The fusion peptides contract, pulling the membranes together.

Endnotes

1. Note a: G+ = Gram-positive; G− = Gram-negative. Return to reference a
2. Note b: CDC reported cases for 2016. Return to reference b
3. Note b: CDC reported cases for 2016. Return to reference b
4. Note b: CDC reported cases for 2016. Return to reference b
5. Note b: CDC reported cases for 2016. Return to reference b
6. Note b: CDC reported cases for 2016. Return to reference b
7. Note c: Total estimated current cases. Nonreportable disease. Return to reference c
8. Note c: Total estimated current cases. Nonreportable disease. Return to reference c
9. Note c: Total estimated current cases. Nonreportable disease. Return to reference c

26.5 Cardiovascular and Systemic Infections

The cardiovascular system, which includes the heart, arteries, veins, and capillaries, delivers oxygen, nutrients, and immune system components to all tissues of the body. There are pathogens that can directly infect the heart or the endothelial cells lining blood vessels. However, the blood itself can also become infected or serve as a mass transit system to spread pathogens throughout the body. Pathogens disseminated in this way can cause infections in many different organ systems. We examine both types of infections in this section.

Infections of the cardiovascular system include septicemia, endocarditis (inflammation of the heart's inner lining (**Fig. 26.30**), pericarditis (inflammation of the heart's outer lining), myocarditis (inflammation of heart muscle), and, possibly, atherosclerosis (deposition of fatty substances along the inner lining of arteries). These are all life-threatening diseases.

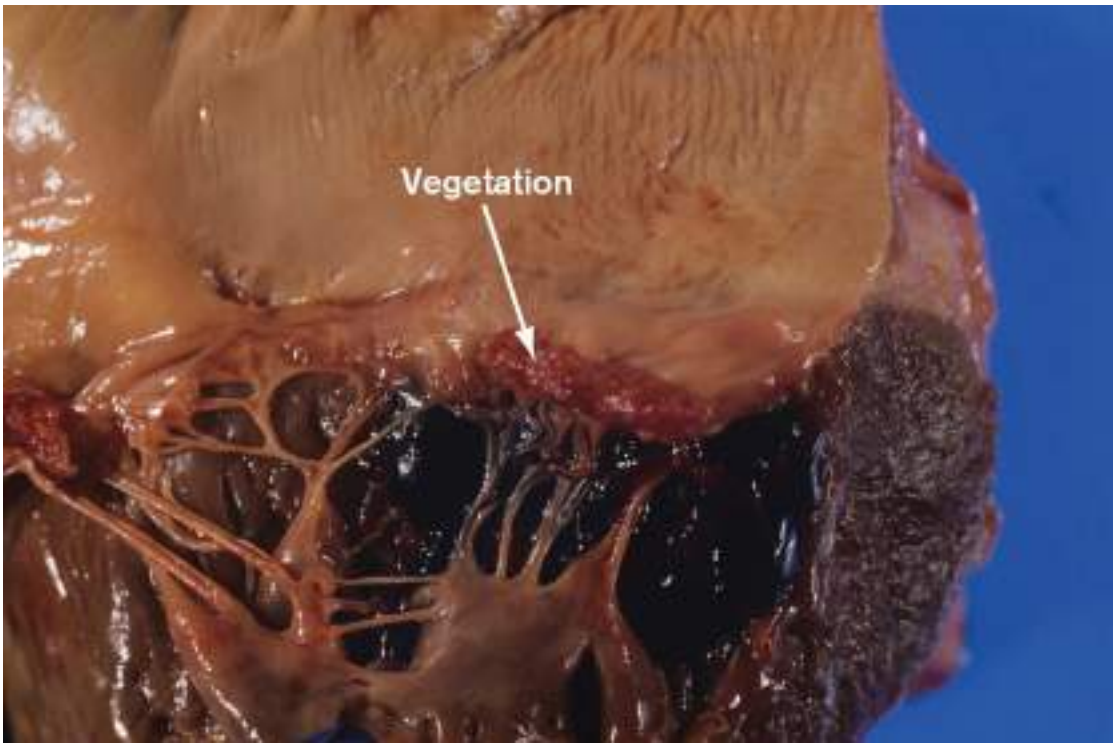


FIGURE 26.30 ■ View of bacterial endocarditis. Close-up of mitral valve endocarditis, showing bacterial vegetation.
DR. E. WALKER/SCIENCE SOURCE

Septicemia is, by strict definition, the presence of bacteria or viruses in the blood. The presence of viruses is a condition more specifically called viremia , while bacteria in the circulation is more specifically called bacteremia . In practice, however, the terms "septicemia" and "bacteremia" are often used interchangeably. Septicemia can develop from a local tissue infection situated anywhere in the body. Once in the bloodstream, bacteria can travel to other organs and cause infections there. To prevent septicemia, regional lymph nodes waiting to receive organisms from the initial infection site recruit massive numbers of neutrophils to ambush the bacteria when they arrive (Special Topic 26). Should some of the organisms escape the lymph node, blood factors such as complement can nonspecifically kill many types of bacteria that enter the blood. Despite these failsafe mechanisms, Gram-positives, Gram-negatives, aerobes, and anaerobes can all produce septicemia under the right conditions.

Endocarditis can be either viral or bacterial in origin. It can be a consequence of many bacterial diseases, such as brucellosis, gonorrhea, psittacosis, staphylococcal and streptococcal infections, candidiasis, and Q fever (*Coxiella*). Among the many viral causes are coxsackievirus, echovirus, Epstein-Barr virus, and HIV. Bacterial infections of the heart are always serious. Viral infections, although common, are rarely life-threatening in healthy individuals and are usually asymptomatic.

Case History: Bacterial Endocarditis

Elizabeth was 38 years old and had a history of mitral valve prolapse (a common congenital condition in which a heart valve does not close properly). She was also on immunosuppressive therapy following a kidney transplant. Recently, Elizabeth was admitted to the hospital complaining of fatigue, intermittent fevers for 5 weeks, and headaches for 3 weeks—symptoms the physician recognized as possible indications of endocarditis. Elizabeth reported having had a dental procedure a few weeks prior to the onset of symptoms. A sample of her blood was cultured in a liquid bacteriological medium. The culture grew Gram-positive cocci, which turned out to be Streptococcus mutans *, a member of the viridans streptococci. With the finding of bacteria in the bloodstream, the diagnosis of bacterial endocarditis was confirmed. Elizabeth began a 1-month course of intravenous penicillin G and gentamicin therapy and eventually recovered to normal health.*

Endocarditis (inflammation of the inner lining of the heart) is traditionally classified as acute or subacute, depending on the pathogenic organism involved and the speed of clinical presentation. Subacute bacterial endocarditis (SBE) has a slow onset with vague symptoms. It is usually caused by bacterial infection of a heart valve (**Fig. 26.30**). SBE infections are usually (but not always) caused by a viridans streptococcus from the oral microbiota (for example, *Streptococcus mutans* , a common cause of dental caries). "Viridans streptococci" is a general term used for streptococci whose colonies produce green alpha hemolysis on blood agar ("viridans" is from the Greek *viridis* , "green"). Many patients who develop infective endocarditis have mitral valve prolapse (20%) or mitral valve damage from rheumatic fever (30%). Also at high risk are intravenous drug abusers or patients who develop hospital-acquired (nosocomial) infections.

Subacute bacterial endocarditis can begin at the dentist's office, as it did in the case history presented here, although it very rarely does (our patient was also immunosuppressed). Following a dental procedure (such as tooth restoration) or even while brushing your teeth, oral bacteria can transiently enter the bloodstream and circulate. *Streptococcus mutans* , a member of the normal oral microbiome, can become lodged onto damaged heart valves, grow as a biofilm, and secrete a thick glycocalyx coating that encases the microbes and forms a vegetation on the valve, damaging it further. If untreated, the condition can be fatal within 6 weeks to a year.

A rapidly progressive (acute) and highly destructive infection can develop when more virulent organisms, such as *Staphylococcus aureus* , gain access to cardiac tissue. Symptoms of acute endocarditis include fever, pronounced valvular regurgitation (backflow of blood through the valve), and abscess formation.

Most patients with subacute bacterial endocarditis present with a low-grade fever that lasts several weeks. They also complain of nonspecific symptoms, such as cough, shortness of breath, joint pain, diarrhea, and abdominal or flank pain. Endocarditis is suspected in any patient who has a heart murmur and an unexplained fever for at least a week. It should also be considered in an intravenous drug abuser with a fever, even in the absence of a murmur. In either case, definitive diagnosis requires blood cultures that grow bacteria. Blood cultures involve taking samples of a patient's blood from two different locations (such as two different arms). Once collected, the blood is added to liquid culture medium (two bottles per site) and incubated at 37°C. One bottle should be incubated aerobically, the other anaerobically. Growth of the same organism in cultures taken from two body sites rules out inadvertent contamination with skin microbes, which would likely yield growth in only one culture.

Curing endocarditis is difficult because the microbes are usually ensconced in a nearly impenetrable glycocalyx. Consequently, eradicating microorganisms from the vegetations almost always requires hospitalization, where high doses of intravenous antibiotic therapy can be administered and monitored.

Antibiotic therapy usually continues for at least a month, and in extreme cases, surgery may be necessary to repair or replace the damaged heart valve.

Patients with heart valve prolapse should not shy away from the dentist, however. As long as a healthy immune system is in place, the risk of infection is low. In fact, maintaining good oral hygiene can keep the risk of developing infectious endocarditis very low. Immunocompromised patients, on the other hand, are at increased risk and should be treated prophylactically with oral amoxicillin or azithromycin 1 hour before a procedure to kill oral bacteria that enter the bloodstream. Note, too, that prosthetic heart valves can develop endocarditis (usually caused by *Staphylococcus aureus*). The treatment of prosthetic valve endocarditis often requires valve replacement.

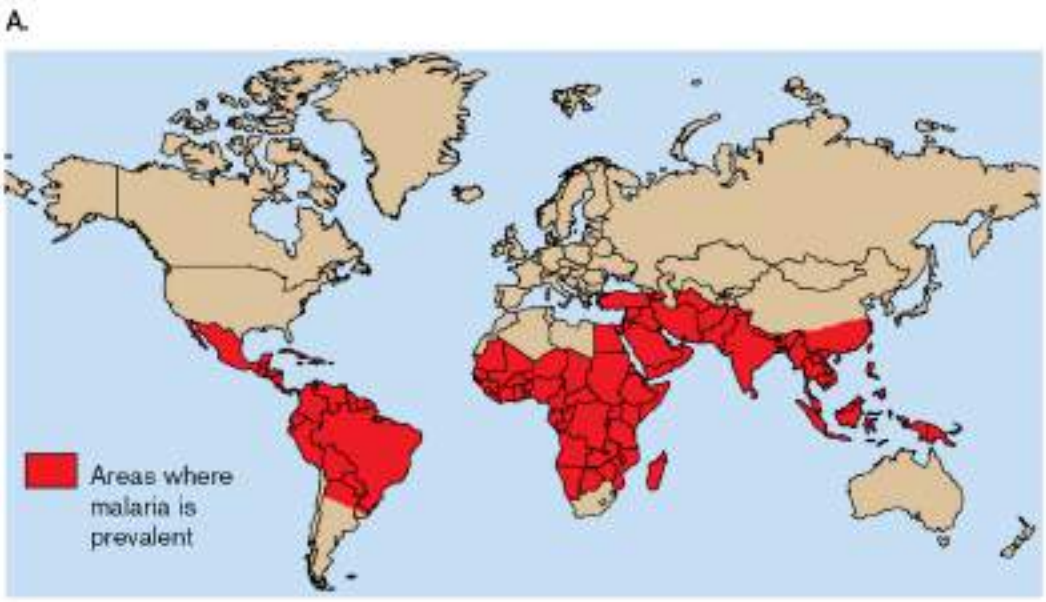
Viruses such as adenovirus and some enteroviruses can also cause endocarditis, as well as a condition known as myocarditis, an inflammation of the heart muscle.

Thought Question

26.10 A patient presenting with high fever and in an extremely weakened state is suspected of having septicemia. Two sets of blood cultures are taken from different arms. One bottle from each set grows *Staphylococcus aureus* , yet the laboratory report states that the results are inconclusive. New blood cultures are ordered. What would make these results inconclusive?

Malarial Parasites Target Red Blood Cells

Malaria is the most devastating infectious disease known. Each year, 300–500 million people develop malaria worldwide, and 1–3 million of these people, mostly children, die. In the United States only about a thousand cases occur annually, and almost all are acquired as a result of international travel to endemic areas (**Fig. 26.31A**). Once again, this correlation illustrates the diagnostic value of knowing a patient's travel history.



B.

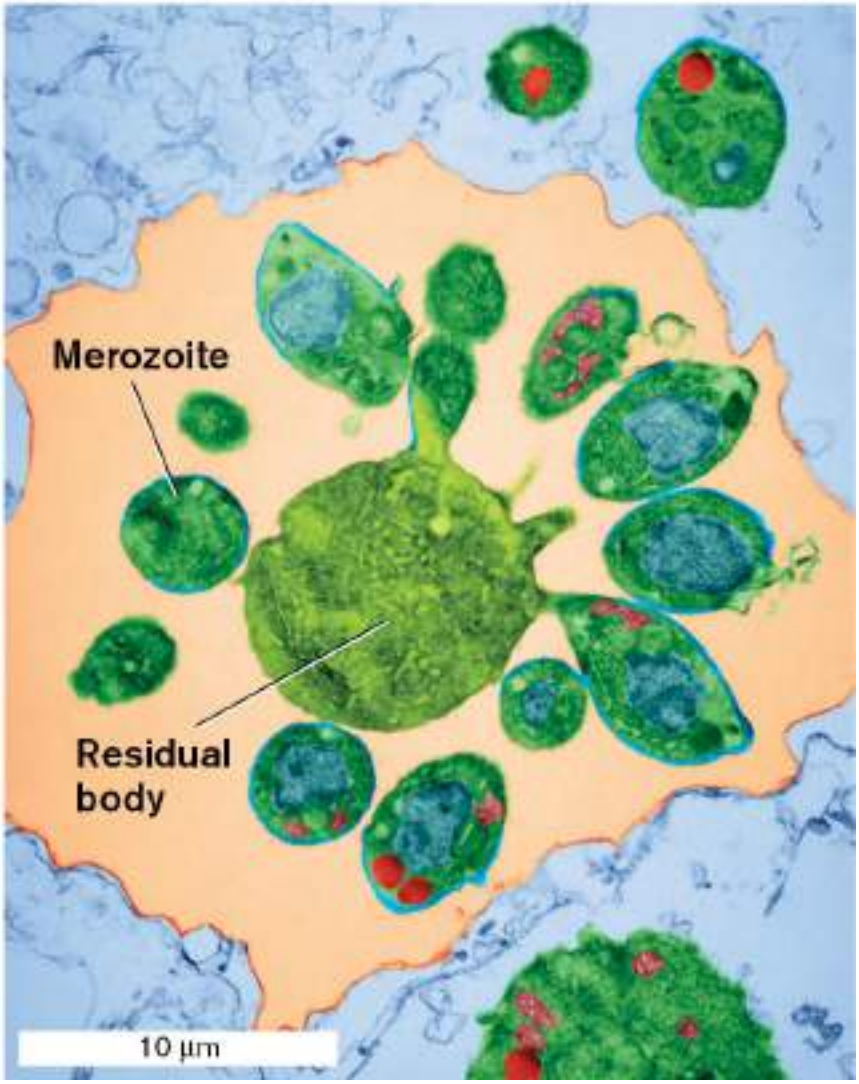


FIGURE 26.31 ■ Malaria is a major disease worldwide. A. Endemic areas of the world where malaria is prevalent. **B.** *Plasmodium falciparum* schizont after completion of division (colorized TEM). A residual body of the organism (yellow-green) is left over after division. The erythrocyte has lysed and only a ghost cell remains; no cytoplasm is seen surrounding the merozoites just being released. Free merozoites are seen outside the membrane.
DENNIS KUNKEL MICROSCOPY/SCIENCE SOURCE

SPECIAL TOPIC 26 How Neutrophils Ambush *Staphylococcus aureus* in a Lymph Node

Every day, bacteria breach the human skin barrier through cuts, abrasions, insect bites, and burns. Yet in healthy people these pathogens rarely disseminate from the initial site of infection to the

systemic circulation. This inability to spread seems odd, since bacteria always arrive at the site of infection well before neutrophils do. Yet the bacteria rarely make it into the bloodstream to cause sepsis or infect other sites. What stops them? Paul Kubes's lab (University of Calgary), with funding from the Canadian Institute of Health Research, found that macrophages, obvious gatekeepers that reside at infection sites or in regional lymph nodes, can slow dissemination—but not by much. Could there be an alternative intercept strategy?

One day, Ania Bogoslowski (**Fig. ST 26.1**), a novice graduate student in the Kubes laboratory, infected a mouse's footpad with *Staphylococcus aureus* and examined the lymph nodes. She found that the organisms had traveled to the regional lymph nodes behind the knee (popliteal lymph nodes, or popLNs) but no farther (**Fig. ST 26.2A**). Why didn't they break into the circulation? Bogoslowski examined the nodes using in vivo microscopy (IVM) and found that, within 5–6 hours of infection, neutrophils were streaming into the nodes, increasing in number from 1,000 per node to over 250,000. IVM enables the observation of processes occurring in a live animal. **Figure ST 26.2B** shows the increase in neutrophils after just 4 hours. The strategy seems to be this: Get neutrophils to the lymph node quickly, and wait for lymph to bring the microbes to them. This way the neutrophils can ambush, rather than chase, any pathogens attempting to disseminate.

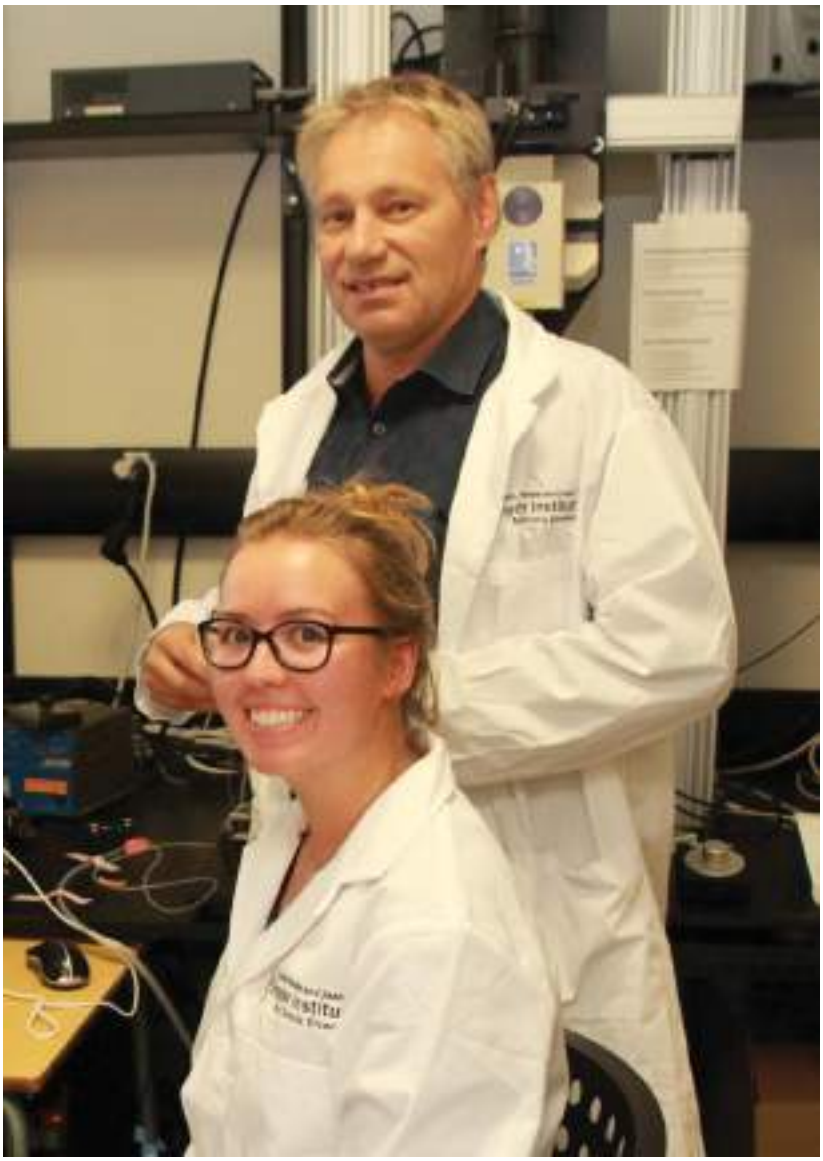


FIGURE ST 26.1 ■ Ania Bogoslowski (seated) and Paul Kubes study the innate immune response to infection.
PHOTO BY CAITLYN MACQUEEN

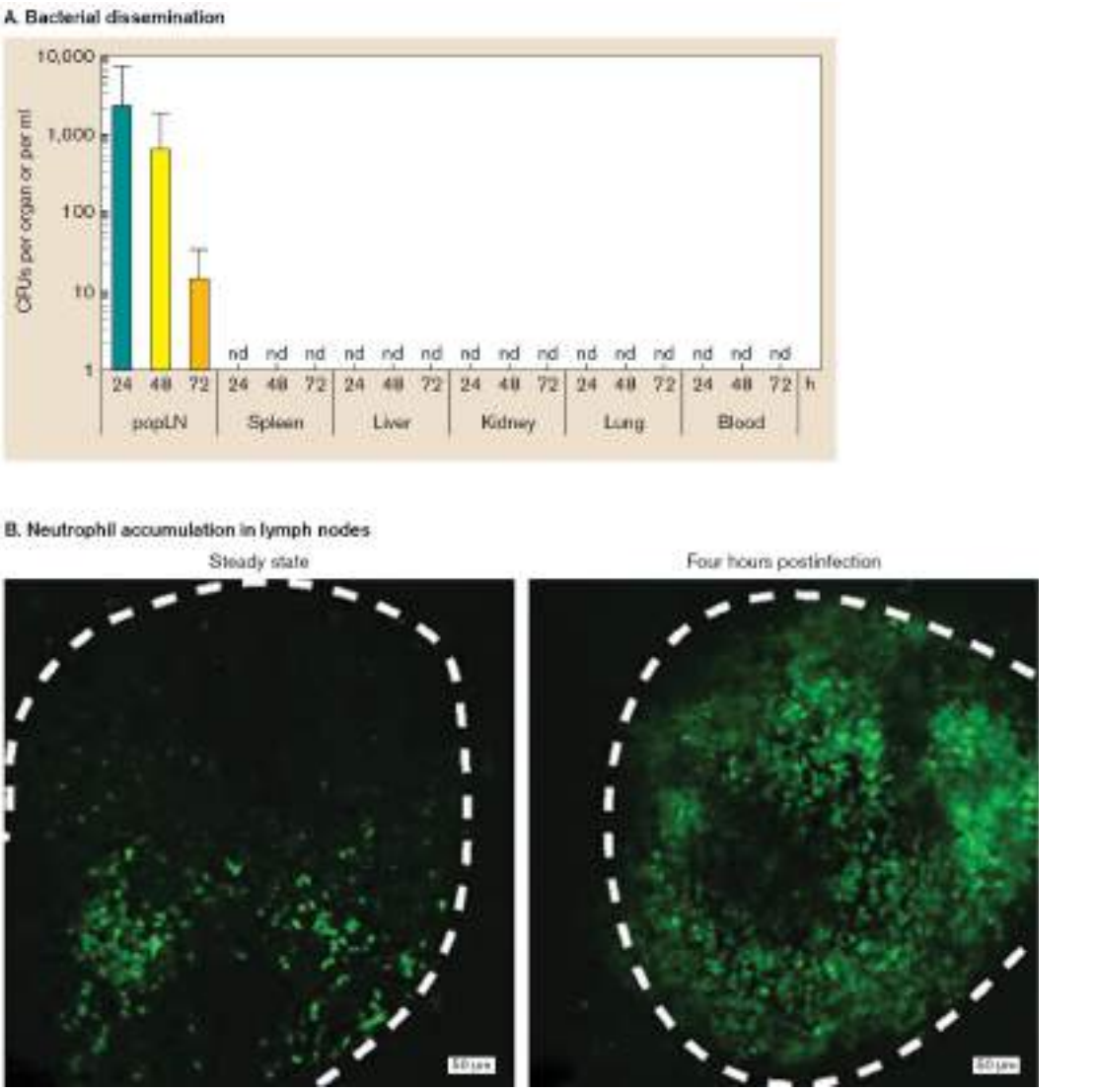


FIGURE ST 26.2 ■ Neutrophil recruitment to popliteal lymph nodes (popLNs) stops *S. aureus* dissemination. A. Bacterial dissemination from a footpad infection site. Data represent counts of colony-forming units (CFUs) of *Staphylococcus aureus* in various organ systems 24, 48, and 72 hours after initial infection (mean ± standard deviation; nd = none detected). **B.** In vivo microscopy of neutrophils present in the lymph node before and 4 hours after footpad infection. Outline of node is marked with a dotted line. Steady-state control shows neutrophils present in an uninfected node.

Source: Modified from Ania Bogoslowski et al. 2018. *PNAS* **115** :2449–2454, fig. 1A.
ANIA BOGOSLOWSKI ET AL. 2018. *PNAS* **115** :2449–2454, FIG. 1B.

Bogoslowski and colleagues showed that the neutrophils migrated into the nodes from the bloodstream, passing through tiny balloon-like structures called high endothelial venules spaced along capillaries situated within the node. But what called the neutrophils to the lymph node? It wasn't the bacteria; neutrophils swarmed to the node even when heat-killed bacteria were injected into the footpad. Macrophages were not involved, since deleting them did not affect neutrophil recruitment. The scientists then examined complement factor C5a, which can also act as a chemoattractant for neutrophils (see Section 23.6). When they blocked C5a receptors

(C5aR) on neutrophils with anti-C5aR antibody, neutrophil recruitment to the lymph nodes stopped (**Fig. ST 26.3**).

Condition	Neutrophils/LN
Phosphate-buffered saline	1.6×10^{5}
C5aR inhibitor	$<1\times10^{1}$

FIGURE ST 26.3 ■ Complement factor C5a recruits neutrophils to the regional lymph node after infection. Mice were treated with phosphate-buffered saline (control) or with blocking antibody to C5aR.

Source: Modified from Ania Bogoslowski et al. 2018. *PNAS* **115** :2449–2454, fig. 3E.

Bogoslowski proposes that a lot of C5a is formed at the site of infection (footpad). The edema that forms in response to the infection causes fluid containing C5a to move from the footpad through the lymphatic vessels to the regional lymph node. The complement factor arrives at the node well before bacteria do and can form a chemotactic gradient that lures neutrophils into the structure to await the arrival of bacteria. The strategy seems to hold also for other pathogens known to cause neutrophil recruitment to regional lymph nodes (*Pseudomonas aeruginosa* and *Mycobacterium bovis* , for instance).

In a follow-up study, the authors discovered that a subset of neutrophils, much like lymphocytes, can recirculate through lymph nodes in a random hunt for pathogens. Those patrolling neutrophils, combined with C5a recruitment, result in neutrophils swarming into a node about to be inundated with bacteria.

RESEARCH QUESTION

How would you use flow cytometry to confirm the in vivo microscopy results? Search the Internet for antigens you would use to screen for neutrophils and draw out (graphically) the results of the flow cytometry experiment.

Bogoslowski, Ania, Eugene C. Butcher, and Paul Kubes. 2018. Neutrophils recruited through high endothelial venules of the lymph nodes via PNAd intercept disseminating *Staphylococcus aureus* . *Proceedings of the National Academy of Sciences USA* **115** :2449–2454.

Bogoslowski, Ania, Sathi Wijeyesinghe, Woo-Young Lee, Chien-Sin Chen, Samer Alanani, et al. 2020. Neutrophils recirculate through lymph nodes to survey tissues for pathogens. *The Journal of Immunology* 204:2552–2561. https://doi.org/10.4049/jimmunol.2000022 .

The disease is caused by four species of *Plasmodium* : *P. falciparum* (the most deadly), *P. malariae* , *P. vivax* , and *P. ovale* . The life cycle of *Plasmodium* , discussed in detail in Chapter 20 , is complex and involves two cycles: an asexual erythrocytic cycle in the human and a sexual cycle in the mosquito (see Fig. 20.39).

In the erythrocytic cycle, an infected female *Anopheles* mosquito bites the victim and injects a small amount of saliva containing *Plasmodium* into the bloodstream. The haploid sporozoites go directly to the liver and undergo asexual fission to produce merozoites. The merozoites attach to and penetrate red blood cells, where *Plasmodium* consumes hemoglobin and enlarges into a trophozoite. The protist nucleus divides so that the cell, now called a schizont, contains up to about 20 nuclei. The schizont then divides to make the smaller, haploid merozoites (**Fig. 26.31B**). The glutted red blood cell eventually lyses, releasing merozoites that can infect new red blood cells (see Fig. 20.39).

Sudden, synchronized release of the merozoites and red blood cell debris triggers the telltale symptoms of malaria: violent, shaking chills followed by high fever and sweating. The erythrocytic cycle and, thus, the symptoms repeat every 48–72 hours. After several cycles, the patient goes into remission lasting several weeks to months, after which there is a relapse.

Much of the research on malaria focuses on relapse. Why does the immune system fail to eliminate the parasite after the first episode? When *Plasmodium* invades the red blood cells, it lines the blood cells with the protein PfEMP1 that causes red blood cells (RBCs) to stick to blood vessels, removing the parasite from circulation. But the protein cannot protect the parasite from patrolling macrophages, which eventually detect the invader and recruit other immune cells to fight it. However, a fraction of each generation of parasite expresses a different version of PfEMP1 that the immune system never encountered. In its new disguise, *Plasmodium* can invade more red blood cells and cause another wave of fever, headaches, nausea, and chills. The body now has to repeat its recognition and attack responses all over again. The parasite has 60 of these cloaking genes, called *var* , that can be turned on and off individually, changing the organisms' antigenic structure, like a criminal repeatedly changing disguises to elude police.

The *var* genes are regulated by chromosome packaging, which unwraps one gene for expression while packing away inactive genes. DNA can be encased so securely that transcription proteins cannot access the packed nucleic acid in a process known as epigenetic silencing. Epigenetic protein modifications (acetylation or methylation) alter the affinity of histones toward different regions of the plasmodial chromosomes. Becoming immune to all the types of malaria can take upwards of 5 years and requires constant exposure; otherwise immunity is lost. Many children afflicted with malaria do not live long enough to gain immunity to the disease in all its forms.

Diagnosis of malaria involves microscopic demonstration of the protist within erythrocytes (Wright stain) or serology to identify antimalarial antibodies. Treatment regimens include artemisinin, whose mechanism of action is unclear; chloroquine or mefloquine, which kills the organisms in their erythrocytic asexual stages; and primaquine, effective in the exoerythrocytic stages by disrupting *Plasmodium* mitochondria. These antimalarial drugs are also given prophylactically to persons traveling to endemic areas. Which drug is given depends on the destination.

The chloroquine family of drugs prevents the detoxification of heme generated from hemoglobin digestion. Malaria parasites accumulate hemoglobin released from red blood cells in plasmodial lysosomes. Lysosomal enzymes digest the hemoglobin, and the parasite uses the amino acids to grow. However, the heme released is toxic. The organism normally detoxifies heme via polymerization, which produces a black pigment. Many antimalarial drugs, such as chloroquine, prevent polymerization by binding to the heme. As a result, the increased iron level (from heme) kills the parasite. Unfortunately, *Plasmodium* has been developing resistance to these drugs, forcing the development of new ones to take their place.

As of 2021, a vaccine for malaria called RTS,S has finally been approved for use by the World Health Organization. The vaccine is designed to defend against the first stages of the disease, when sporozoites first enter the bloodstream before they invade the liver. RTS,S is a protein in which the carboxyl terminus of the *P. falciparum* circumsporozoite protein (CS) is fused to the hepatitis B surface antigen (HBsAg). Circumsporozoite protein is prevalent on the surface of sporozoites. When expressed, the CS-HBsAg chimeric protein, mixed with free HBsAg, assembles into particulate structures; when

injected, these structures can induce anti-circumsporozoite antibodies. The antibodies bind to sporozoites, after which serum complement attaches to the Fc regions of those antibodies, activates, and kills the sporozoites. Although it is 50% effective against severe malaria during the first year, by the fourth year the vaccine, unfortunately, has almost no effect.

While efforts continue toward making an effective, long-lasting vaccine, novel strategies to control the spread of malaria are also being tested. Approaches include using anti-mosquito bacteria to eradicate mosquito vectors, and a genetic approach, called gene drive, designed to eliminate female mosquitoes. Female mosquitoes are targeted because only female mosquitoes take blood, which they need to make eggs. In one gene drive approach, a CRISPR-Cas9 system would be introduced into the mosquito Y chromosome. The guide RNAs of this system will direct the cleavage of sequences within the X chromosome. As a result, sperm from these males should all contain the Y chromosome. No male X chromosomes will be passed to eggs, so no female mosquitoes will be produced. Various gene drive systems are currently being tested.

Bear in mind that we have described only selected organisms that cause cardiovascular infections; there are many more (for example, *Rickettsia typhi*).

Note: Babesiosis is an emerging disease caused by a protozoan (*Babesia microti*) that, like *Plasmodium* , infects red blood cells. *B. microti* is transmitted by the deer tick, the same insect that transmits the agent for Lyme disease. Typically, babesiosis is a mild, flu-like disease, but in its severe form it can present with symptoms similar to those of malaria.

Systemic Infections

Many pathogenic bacteria can produce septicemia as a way to disseminate throughout the body and infect other organs. These organisms cause what are considered systemic infections.

Case History: The Plague

A 25-year-old New Mexico rancher was admitted to an El Paso hospital because of a 2-day history of headache, chills, and fever (40°C; 104°F). The day before admission, he had begun vomiting. The day of admission, an orange-sized, painful swelling in the right groin area was noted (***Fig. 26.32A*** *). A lymph node aspirate and a smear of peripheral blood were reported to contain Gram-negative rods that exhibited bipolar staining (* ***Fig. 26.32B*** *). The patient's white blood cell count was 24,700 per microliter (normal is 5,000–10,000), and his platelet count was 72,000 per microliter (normal is 130,000–400,000). In the 2 weeks prior to becoming ill, the patient had trapped, killed, and skinned two prairie dogs, four coyotes, and one bobcat. The patient also mentioned that he had cut his left hand shortly before skinning a prairie dog. The clinical laboratory isolated a Gram-negative rod from blood cultures. PCR and biochemical testing identified the organism as* Yersinia pestis *, the bacterium that causes plague. The severely ill rancher received an antibiotic cocktail of gentamicin and tetracycline, and he eventually recovered after 6 weeks in intensive care.*

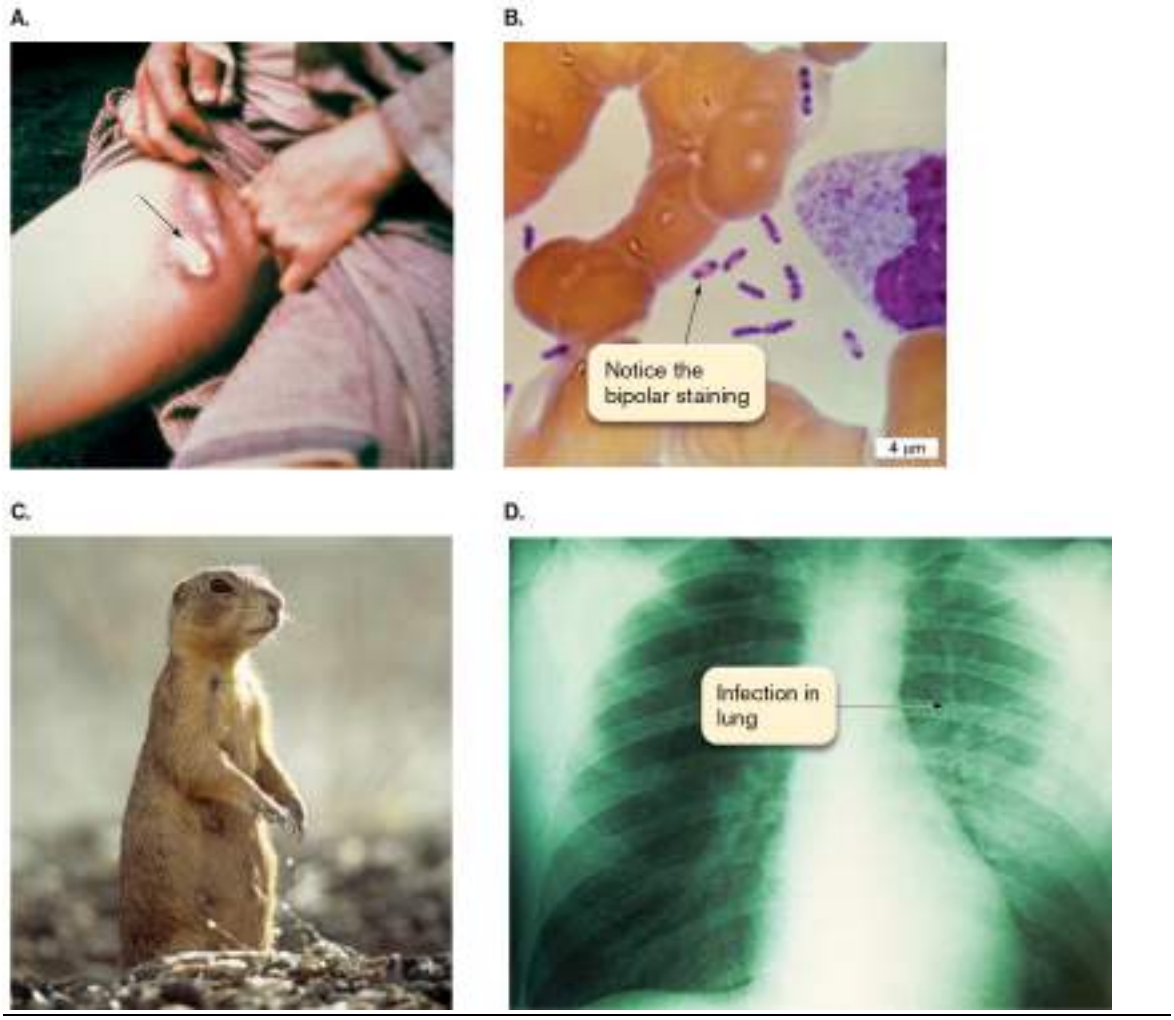


FIGURE 26.32 ■ The plague. A. Classic bubo (swollen lymph node) of bubonic plague. **B.** *Yersinia pestis* , bipolar staining (length 1–3 μm). **C.** Prairie dogs are often hosts to fleas that carry plague bacilli. **D.** X-ray of pneumonic plague, showing pulmonary infection.

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Plague is caused by the bacterium *Yersinia pestis* , which can infect both humans and animals. During the Middle Ages, the disease known as the Black Death decimated over a third of the population of Europe. Such was the horror it evoked that invading armies would actually catapult dead plague victims into embattled fortresses. This was probably the first reported case of biowarfare.

Y. pestis is present in the United States and is endemic in 17 western states. Typically, the bite of infected fleas transmits the microbe between animals such as rats and even prairie dogs (**Fig. 26.32C**). **Figure 26.33** illustrates the various infection cycles of the plague bacillus. Humans are not part of the natural infection cycle. In the absence of an animal host, however, the flea can take a blood meal from humans and thereby transmit the disease to them. During the Middle Ages, urban rats venturing back and forth to the countryside became infected by the fleas of wild rodents that served as a reservoir. Upon returning to the city, the rat fleas passed the organism on to other rats, which then died in droves. The rat fleas, deprived of their normal meal, were forced to feed on city dwellers, passing the disease on to them.

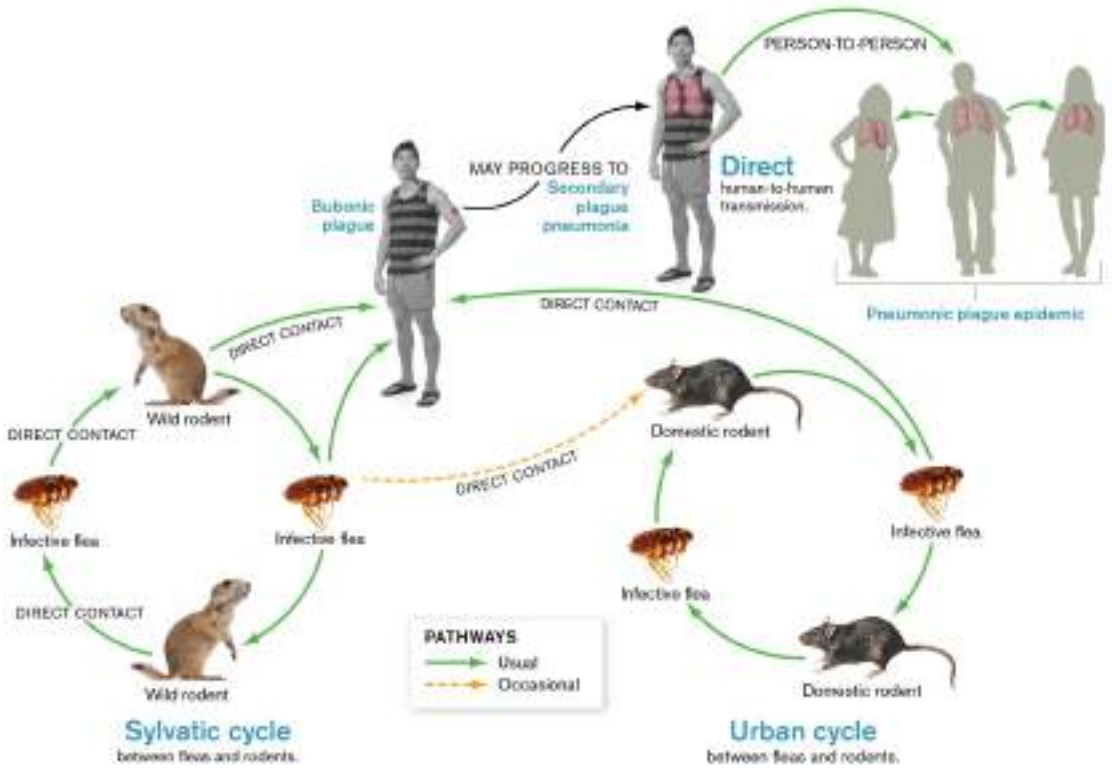


FIGURE 26.33 ■ The cycles of plague. The sylvatic cycle occurs in the wild, where fleas transmit the organism between rodents. An accidental interaction with urban rats can trigger a similar urban cycle. Humans can be infected through contact with infected fleas coming from either cycle. Flea bite transmission initiates bubonic plague symptoms that can progress to pneumonic plague. Because it is highly infectious, pneumonic plague can cause epidemic spread of the disease.

Individuals bitten by an infected flea or accidentally infected through a cut while skinning an infected animal will first exhibit the plague form known as bubonic plague . Bubonic plague develops as the organism moves from the site of infection to the regional lymph nodes, producing characteristically enlarged nodes called buboes (see **Fig. 26.32A**). From the lymph nodes, the pathogen can enter the bloodstream, causing septicemic plague . In this phase the patient can go into shock (sudden drop in blood pressure) from the massive amount of endotoxin in the bloodstream. In the case history, the rancher's low platelet count (thrombocytopenia) was an indication that his platelets were being consumed by the considerable clotting taking place. Neither bubonic nor septicemic plague is passed from person to person. As the organism courses through the bloodstream, however, it will invade the lungs and produce pneumonic plague (see **Fig. 26.32D**), which can be easily transmitted from person to person through aerosol droplets generated by coughing.

Pneumonic plague is the most dangerous form of the disease because it can kill quickly and spread rapidly through a population. Pneumonic plague is so virulent that an untreated patient can die within 24–48 hours. The rapid spread of plague during the Middle Ages was most likely the result of person-to-person transmission through respiratory aerosols.

Y. pestis has numerous virulence factors. For instance, YadA is a surface adhesin that binds collagen. Another factor, the F1 protein capsule surface antigen, plays a part in blocking phagocytosis in mammalian hosts. Certain biofilms formed by *Y. pestis* are also important. An extracellular matrix synthesized by *Y. pestis* produces an adherent biofilm in the flea midgut that contributes to flea-to-mammal transmission. The biofilm blocks the flea's digestion, making the flea feel "starved" even after a blood meal. Therefore, the flea jumps from host to host in a futile effort to feel full. As the flea tries

to take a blood meal, the blockage causes the insect to regurgitate bacteria into the wound. This curious effect of *Y. pestis* on the insect vector is another unique aspect of how plague spreads so quickly.

Y. pestis also uses type III secretion systems to inject virulence proteins (YopB and YopD) into host cell membranes. Unlike *Salmonella* , which uses type III–secreted proteins to gain entrance into host cells, *Y. pestis* is not primarily an intracellular pathogen, although it can survive in macrophages. Injection of the Yop proteins disrupts the actin cytoskeleton, thereby helping the organism evade phagocytosis. By evading phagocytosis, the organism avoids triggering an inflammatory response and produces massive tissue colonization.

The last major outbreak of plague in Europe occurred in 1772. Why the disease disappeared from Europe is unclear, but part of the reason was probably human intervention. Long before doctors understood how germs could cause disease (1800s), Europeans recognized that plague was contagious and could be carried from one area to another. Beginning in the 1600s, governments established a medical boundary, or *cordon sanitaire* , between Europe and the areas to the east from which epidemics came. Ships traveling west from the Ottoman Empire were forced to wait in quarantine before passengers and cargo could be unloaded. Those who attempted to evade medical quarantine were shot. We don't shoot them anymore, but we do quarantine groups of people exposed to dangerous infectious agents (Ebola virus, for example). Anyone who gets sick is then placed in isolation. Because the SARS-CoV-2 virus was not as lethal as Ebola, protocols for quarantine and isolation during the COVID-19 pandemic varied across the world. Some countries imposed strict lockdown procedures; others, such as the United States, relied mostly on shelter-in-place or self-imposed home quarantine for individuals exposed to the virus.

Sepsis and Toxic Shock

Many bacterial pathogens can, under the right circumstances, infect the bloodstream to cause septicemia and ultimately sepsis—a life-threatening condition involving high fever, high white blood cell counts, rapid heart rate and/or rapid breathing, and low platelet counts when severe. The offending bacteria are typically found in the blood (see Chapter 28). Organisms that can cause sepsis include *Neisseria meningitidis* , *Escherichia coli* , *Enterococcus* species, and many others, including *Yersinia pestis* from the preceding case. In severe cases sepsis can progress to septic shock, in which the patient's blood pressure drops to dangerous levels.

Case History: Toxic Shock

In May 2017, a visibly ill 24-year-old woman was taken to the emergency department by her boyfriend, where she complained of diarrhea, high fever (40°C; 104°F), and vomiting. She told the physician that she had become ill 2 days earlier. On examination, the doctor noticed that the woman had very low blood pressure (80/40 mm Hg; normal range 90–130/60–90), a rapid heart rate (122 beats per minute; normal range 60–100), and an erythematous (red) rash on her trunk. These are all signs of septic shock. Because of her deteriorating condition, the patient was admitted to the intensive care unit, where she was immediately given intravenous fluids and broad-spectrum IV antibiotics. Blood cultures taken when she first arrived were negative: No bacteria were found. The woman rallied and left the hospital 4 days later. Patient history taken upon admission revealed that the woman had started her menstrual period 4 days before becoming ill, providing an important clue as to the cause of the disease.

This potential tragedy reflects a larger story that emerged in the late 1970s and early 1980s, when women started dying from this dangerous, new (emerging) disease, now known as toxic shock syndrome. We've since learned that it is caused by certain strains of *Staphylococcus aureus* and *Streptococcus pyogenes* that produce a superantigen type of toxin (toxic shock syndrome toxin, or TSST; see Section 24.3). Why wasn't the disease recognized in previous decades? The answer turned

out to be the use of one brand of superabsorbent tampons (since removed from the market). The tampons produced a rich growth environment for *S. aureus* . So, if the patient was colonized by a TSST-producing strain, huge amounts of toxin were released to circulate in the bloodstream.

Even though the superabsorbent tampons are no longer available, toxic shock syndrome is still sometimes associated with menstruation, as in the case history. Today, however, we recognize that toxic shock syndrome can occur in both men and women and is a possible consequence of any *S. aureus* infection involving a TSST-producing *S. aureus* . The toxin is secreted by *S. aureus* at the infection site and spreads rapidly through the circulation to cause generalized, potentially lethal symptoms. The bacteria usually do not circulate in blood, which explains the negative blood culture in the case history.

Knowledge that a protein toxin was the cause of the disease led to a recommendation that treatment of toxic shock syndrome include the antibiotic clindamycin. As you learn in Chapter 27 , clindamycin is an inhibitor of bacterial protein synthesis. By blocking protein synthesis, clindamycin decreases the amount of TSST made, while other antibiotics (vancomycin, for instance) kill the pathogen. In our case study, the combination saved the woman's life. In Chapter 25 we discuss other weapons that *S. aureus* uses to cause disease.

Case History: Lyme Disease

*Brad, a 10-year-old from Connecticut, developed a fever and a large (8-cm) reddish rash with a clear center (erythema migrans) on his trunk (**Fig. 26.34A**). He also had some left-facial-nerve palsy (partial paralysis of his face). Brad had returned a week previously from a Boy Scout camping trip to the local woods, where he had done a lot of hiking. When asked by his physician, Brad recalled finding a tick on his stomach while in the woods but thought little of it. The doctor ordered serological tests for* Borrelia burgdorferi *(the organism that causes Lyme disease),* Rickettsia rickettsii *(which produces Rocky Mountain spotted fever), and* Ehrlichia equi *(which causes ehrlichiosis). The ELISA test for* B. burgdorferi *antibodies came back positive, confirming a diagnosis of Lyme disease. The boy was given a 2-week regimen of doxycycline (a tetracycline derivative), which resolved the rash and palsy.*

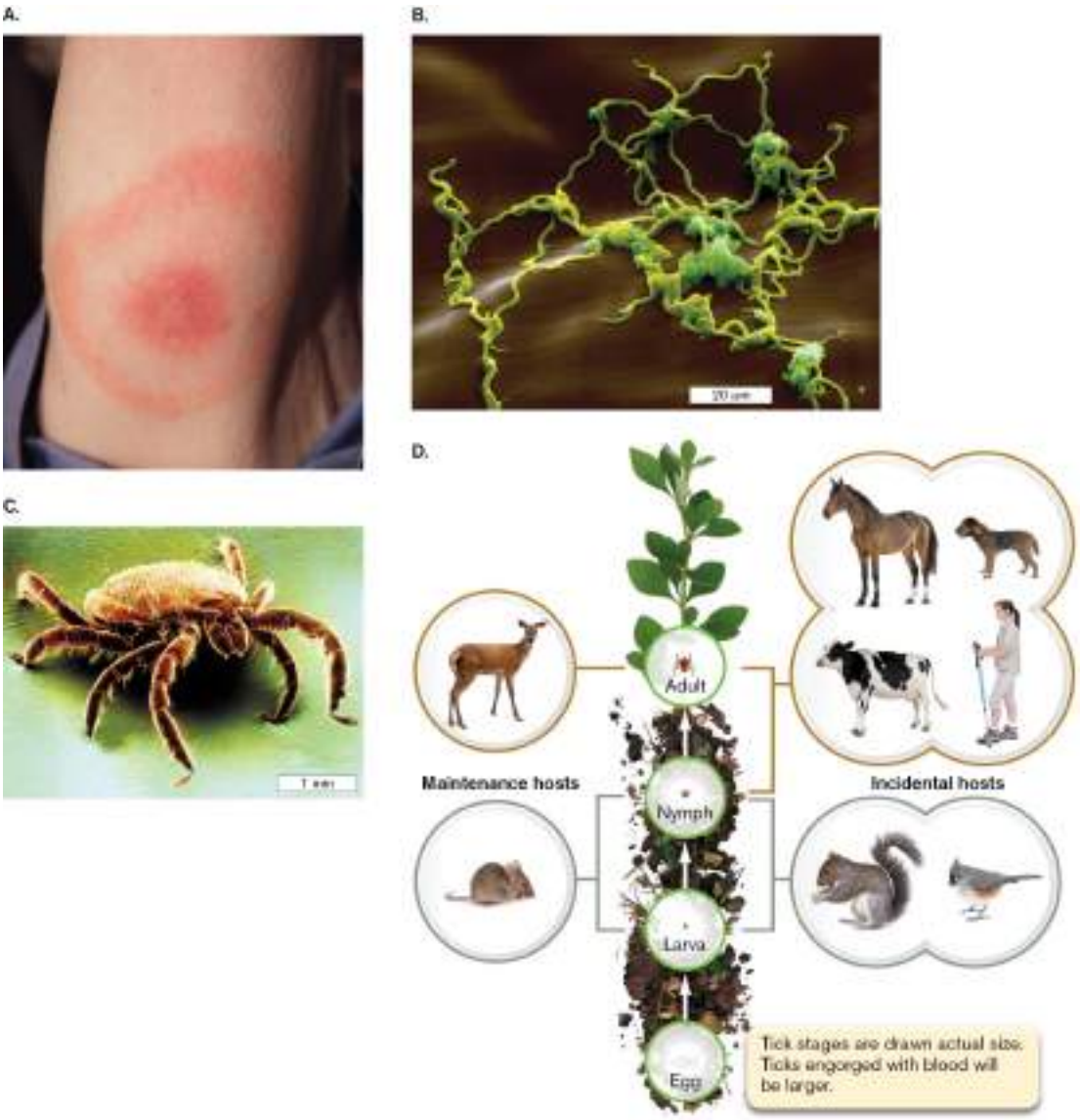


FIGURE 26.34 ■ Lyme disease. A. Erythema migrans rash. **B.** *Borrelia burgdorferi* , the agent of Lyme disease (cell length 5–30 µm; colorized SEM microscopy). **C.** *Ixodes* vector (SEM). **D.** Host associations of *Ixodes scapularis* . The life cycle of the tick from egg to adult takes two years to complete. As the ticks develop, they are attracted to the barberry bush, from which females can transfer to a variety of animals for a blood meal.

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Lyme arthritis was first reported in Lyme, Connecticut, in the 1970s, but the causative organism, *Borrelia burgdorferi* , was not identified until 1982. Since then, Lyme disease (a form of borreliosis) has become the most common vector-borne illness in the United States (approximately 30,000–40,000 new cases per year). The main endemic areas are the northeastern coastal area from Massachusetts to Maryland, Wisconsin and Minnesota, and northern California and Oregon, but the disease has been spreading into the southern states. Lyme disease caused by different *Borellia* species is also common in parts of Europe.

B. burgdorferi is a spirochete (**Fig. 26.34B**) transmitted to humans by ixodid ticks (hard ticks; **Fig. 26.34C** and **D**). In the northeastern and central United States, where most cases occur, the deer tick *Ixodes scapularis* transmits the spirochete, usually during the summer months. In the western United States, *I. pacificus* is the tick vector.

During its nymphal stage (the stage after taking its first blood meal), *I. scapularis* is the size of a poppy seed. Its bite is painless, so it is easily overlooked. Infection takes place when the tick feeds, because the spirochete is regurgitated into the host. However, the organism grows in the tick's digestive tract and takes about 2 days to make its way to the tick's salivary gland, so if the tick is removed before that time, the patient will not be infected. Once the pathogen is transferred to the human, the microbe can travel rapidly via the bloodstream to any area in the body, but it prefers to grow in skin, nerve tissue, synovium (joint lining), and the conduction system of the heart.

Lyme disease has three stages. Similar to syphilis caused by the spirochete *Treponema pallidum* , Lyme disease has three general stages. Stage 1 involves the localized spread of *Borrelia burgdorferi* between 3 and 30 days after the initial exposure. Approximately 75% of patients experience an erythema migrans rash, usually at the site of the tick bite. The appearance of the rash varies but is classically erythematous with central clearing ("bull's-eye" rash). This stage is often associated with constitutional symptoms such as fever, myalgia (muscle pain), arthralgia (joint pain), and headache.

Stage 2 occurs weeks to months after the initial infection as *B. burgdorferi* spreads from blood to other organs. In this stage, the patient can be quite ill with malaise, myalgia, and arthralgia, as well as neurological or cardiac involvement. Common neurological manifestations include Bell's palsy (facial paralysis), inflammation of spinal nerve roots, and chronic meningitis. The most common cardiac manifestation is an irregular heart rhythm.

Stage 3 borreliosis occurs months to years later and can involve the synovium, nervous system, and skin. Arthritis occurs in the majority of previously untreated patients; it is usually intermittent, involves the large joints, particularly the knee, and lasts from weeks to months in any given joint. Joint-fluid analysis typically shows a WBC count of 10,000–30,000 per microliter (normal is fewer than 200). Late neurological involvement may include peripheral neuropathy and encephalopathy, manifested as memory, mood, and sleep disturbances.

Treatment with antibiotics (usually doxycycline) is recommended for all stages of Lyme disease but is most effective in the early stages. Lyme arthritis is typically slow to respond to antibiotic therapy, so treatment lasts from 2 to 4 weeks. However, the disease in some people does not resolve at all; why is not known.

Curiously, 25% of people infected with *B. burgdorferi* never experience erythema migrans, and many infected individuals are also unsure of tick bites. Hence, patients with Lyme disease may present with arthritis as their first complaint. Although this makes diagnosis extremely difficult, knowing that the patient lives in or recently traveled to an endemic area can provide a critical clue.

A startling example of how sinister Lyme disease can be is the case of Kris Kristofferson, a prolific singer, songwriter, and actor, now in his eighties. Kristofferson suffered for years with severe memory loss presumed to be a manifestation of Alzheimer's disease until someone decided to test him for Lyme disease. To his doctor's surprise and relief, the singer tested positive. Kristofferson immediately began antibiotic treatments and has since recovered much of his memory.

Many other bacteria can cause septicemia and systemic illness (Table 26.6). Gram-negative organisms, such as *E. coli* , *Salmonella* Typhi, and *Francisella* , and Gram-positive microbes, such as *Staphylococcus aureus* , *Enterococcus* , and *Bacillus anthracis* , can grow in the bloodstream if they can gain entrance. Even anaerobes that are normal inhabitants of the intestine (for example, *Bacteroides fragilis*) can be lethal if they escape the intestine and enter the blood, as might happen following surgery. This is one reason surgical patients are given massive doses of antibiotics immediately before and after surgery.

TABLE 26.6	Selected Systemic Infectious Diseases				
Disease	**Symptoms**	**Etiological agent** [a]	**Virulence properties**	**Source(s)**	**Treatment**
Lyme disease	Stage 1: rash; stage 2: chills, headache, malaise, systemic involvement; stage 3: neurological changes	*Borrelia burgdorferi* (spirochete)	Antigenic variation, OspE (binds complement)	Deer tick	Penicillin, doxycycline
Brucellosis	Fever, weakness, sweats, splenomegaly, osteomyelitis, endocarditis, others	*Brucella abortis* (G– rod)	Intracellular, growth in monocytes	Animal products, unpasteurized milk	Doxycycline
Leptospirosis	Fever, photophobia, headache, abdominal pain, skin rash, liver involvement, jaundice	*Leptospira interrogans* (spirochete)	Burrowing motility	Urine of infected animals	Penicillins, erythromycin
Epidemic typhus	Chills, fever, headache, muscle pain, splenomegaly, coma	*Rickettsia prowazekii* (G– rod)	Obligate intracellular growth, escapes phagosome	Human louse, flying-squirrel flea	Tetracycline, chloramphenicol
Tularemia	Fever, chills, headache, muscle pain, rash, bacteremia	*Francisella tularensis* (G– rod)	Intracellular	Rabbits, rodents, insect vectors	Gentamicin, streptomycin

TABLE 26.6	Selected Systemic Infectious Diseases				
Typhoid fever	Septicemia, chills, fever, hypotension, rash (rose spots)	*Salmonella* Typhi (G– rod)	Type III secretion, intracellular growth, PhoPQ regulators, Vi antigen capsule	Gallbladder of human carrier	Ciprofloxacin, ceftriaxone
	Septicemia, chills, fever, hypotension	*Salmonella choleraesuis* (G– rod)	Intracellular growth, invasin	Animals, poultry	Ceftriaxone
Vibriosis	Serious with immunocompromised patients; fever, chills, multi-organ damage, death	*Vibrio vulnificus* (G– curved rod)	Cytolysin, capsule	Seawater, raw oysters	Tetracycline plus 3rd-generation cephalosporin
Bubonic plague	Buboes (swollen lymph glands), high fever, chills, headache, cough, pneumonia, septicemia	*Yersinia pestis* (G– rod)	Intracellular growth, type III secretion of YOPs (*Yersinia* outer proteins), phospholipase D, toxin	Rodents, rodent fleas, human respiratory aerosol, potential bioterrorism agent	Streptomycin or tetracycline

Ebola—The Perfect Pathogen or Too Deadly for Its Own Good?

How would you define the perfect pathogen? Would it be an organism that can kill its host with terrifying ease and quickness? If so, Ebola virus would fit the description. Ebola virus, a lipid-enveloped, threadlike RNA virus (*Filoviridae* ; see Fig. 25.4), was first associated with an outbreak of 318 cases of a hemorrhagic disease in Zaire (now the Democratic Republic of the Congo) in 1976. Of the 318 people who contracted the disease, 280 died within days. The disease was characterized by acute (rapid) onset of fever, headache, diarrhea, and severe muscle pains. Some patients exhibited horrible bleeding (hemorrhaging) from multiple orifices (nose, mouth, anus, and vagina) and ultimately died.

The Ebola virus has a frightening reputation. It spreads like wildfire through the body after infection, causing severe hemorrhagic fever, and typically kills 20%–90% of its victims, depending on

the strain involved and the level of care received. Internal bleeding results in shock and acute respiratory distress, leading to death. The major 2014–2016 epidemic of Ebola in western Africa involved 28,683 cases, 40% of whom died (see Chapter 28). Smaller outbreaks have occurred since then; the most recent (2021) was in the Democratic Republic of the Congo. The symptoms of Ebola (and of a related disease caused by the Marburg virus) reflect subversion of the innate immune system, coupled with uncontrolled viral replication, particularly in macrophages and dendritic cells. Ebola virus infection of these cells enhances production of pro-inflammatory cytokines, such as TNF-alpha, and inhibits stimulation of T-cell maturation by dendritic cells. Thus, Ebola infections not only stimulate inflammatory processes leading to tissue damage, they also shut down early immune responses and prevent activation of adaptive immune responses, thereby allowing unfettered viral replication.

Ebola viral proteins and their locations in the virion are shown in **Figure 26.35A** . Ebola VP35 protein is a component of the viral RNA polymerase complex, but it is also a potent inhibitor of host interferon (IFN) production. The cellular response to whichever IFN is made is inhibited by VP24, which blocks the nuclear accumulation of a regulatory protein called STAT1. STAT1 is critical to IFN-stimulated gene expression. These and other strategies enable rapid replication of the virus.

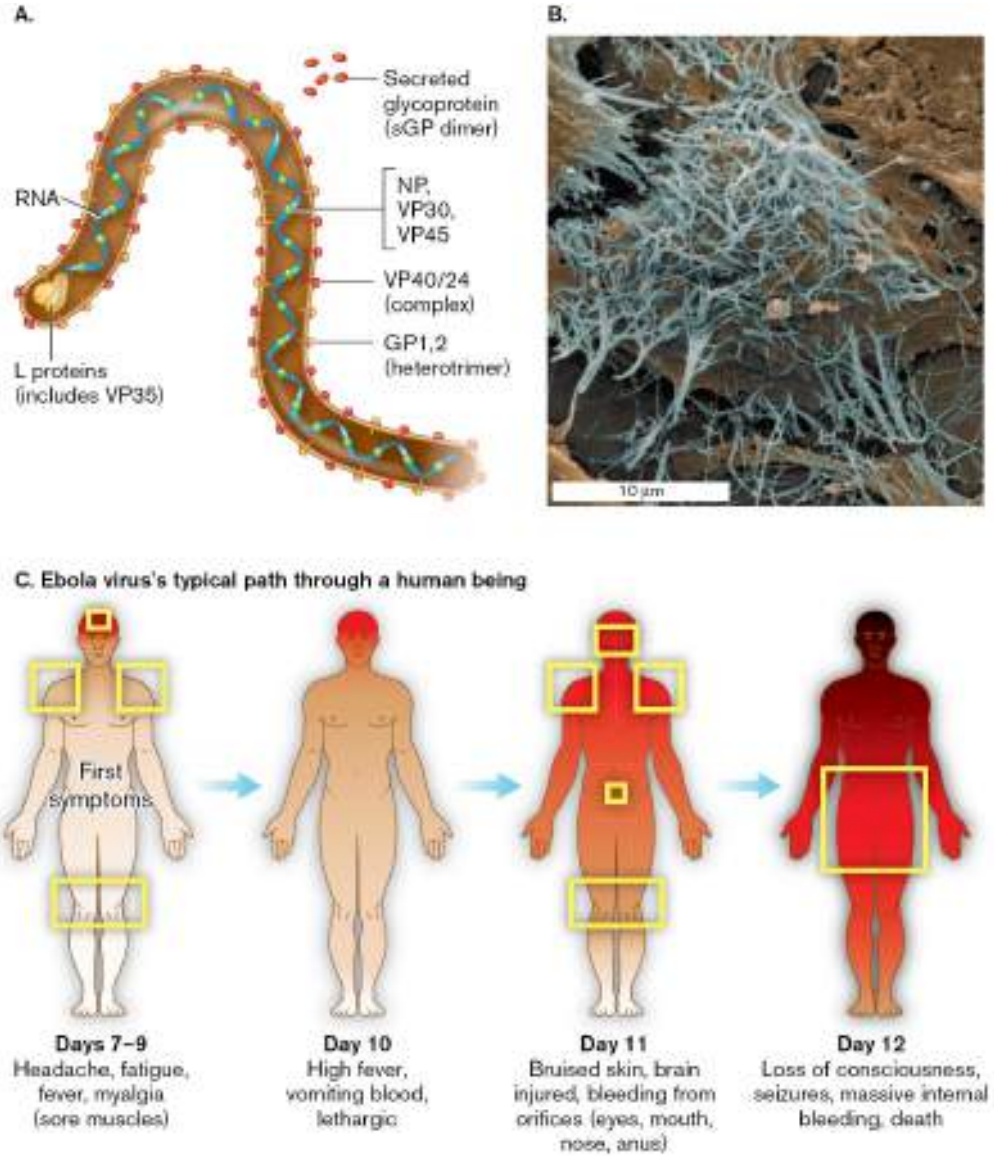


FIGURE 26.35 ■ Ebola virion. A. Composition of the virus. The ribonucleoprotein complex consists of the nucleoprotein (NP), the structural proteins VP30 and VP35, and the virion-associated RNA-dependent RNA polymerase (L proteins). The glycoprotein (GP-sGP) is an integral membrane protein that can be secreted. **B.** Threadlike Ebola virions budding from a cell (center). **C.** Progression of the disease.

Source: Part C modified from http://themindbodyshift.com/index.php/2014/10/16/when-the-threat-of-ebola-hits-home .

KALETSKY, R. L., ET AL. 2009. *PNAS* **106** :2886.

After replicating, Ebola offspring sprout from the cell surface in a mass of tangled threads (**Fig. 26.35B**). These new virions go on to attack new cells, riddling blood vessels and organs with damage as they go. Rapid release of new virions involves subverting another host mechanism, tetherin, designed to slow viral spread. Paul Bates and his colleagues at the University of Pennsylvania discovered that the cell protein tetherin essentially tethers mature virus particles inside a cell so that they are unable to spread. Tetherin is IFN induced and can restrict the spread of structurally diverse enveloped viruses, including HIV (thus, it is part of the innate response). Ebola glycoprotein, however, counteracts tetherin, so that nothing slows down viral spread. The result is rapid release of massive numbers of virus particles that can then quickly spread infection to other organs and tissues.

The outlook for a patient infected with Ebola is typically dire (occasionally a person infected with Ebola virus can develop antibodies but remain asymptomatic). The incubation period is 4–16 days, and death occurs within 7–16 days (**Fig. 26.35C**). With good supportive care, including the replacement of coagulation factors, the mortality rate appears near 20%. In the absence of such care, mortality can reach over 80%. For the latest outbreaks in Africa, the World Health Organization (WHO) has approved use of three experimental treatments and a vaccine. The treatments include a recombinant monoclonal antibody (ZMapp) that has Ebola virus–neutralizing activity, an RNA-dependent RNA polymerase inhibitor, and an RNA chain terminator. The WHO-approved vaccine (ERVEBO) is an attenuated vesicular stomatitis virus engineered to express a glycoprotein from the most lethal Ebola virus (*Zaire ebolavirus*). Neutralizing antibody to this glycoprotein is produced after vaccination. Vaccination efforts in Africa are widespread, but they principally focus on people living in areas ringing an outbreak in order to limit spread of the disease.

Death comes very quickly with this disease, typically before the virus can be transmitted to very many new hosts. Some scientists argue that efficient and quick killing is not the mark of a perfect pathogen. The better pathogen lets its host linger to ensure a home for itself and more opportunity to disseminate. So, why doesn't Ebola die out? Where does it go when it is not infecting humans? The natural ecology of these viruses is largely unknown, although an association with monkeys and/or bats as possible reservoirs is suggested.

To Summarize

- **Blood cultures** are useful in diagnosing septicemia and endocarditis.
- **Septicemia** is caused by many Gram-positive and Gram-negative bacterial pathogens. It can start with the bite of an infected insect, introduction via a wound, escape from an abscess, or penetration of the mucosal epithelium by the pathogen (intestine or vagina) and can lead to disseminated, systemic disease.
- **Endocarditis** can have acute or subacute onsets. **Subacute bacterial endocarditis** is usually an endogenous infection of a heart valve caused by *Streptococcus mutans* .
- **Malaria, caused by *Plasmodium* species** , manifests as repeated episodes of chills, fever, and sweating, owing to the organism's ability to alter the antigenic appearance of its surface proteins and evade the immune response.

- **Plague, caused by *Yersinia pestis*** , has sylvatic and urban infection cycles involving transmission by fleas. The bite of an infected flea leads to bubonic plague. Bubonic plague can progress to septicemic and pneumonic stages. Pneumonic plague can be spread directly from person to person (no insect vector) by **aerosolized respiratory secretions** .
- **Toxic shock syndrome is a sepsis-like, systemic disease caused by an exotoxin (toxic shock syndrome toxin, TSST)** secreted by some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* . It is caused by the circulatory spread of TSST made from bacteria that infect or colonize a localized tissue.
- **Lyme disease** is caused by the spirochete *Borrelia burgdorferi* , which is transmitted from animal reservoirs to humans by the bite of *Ixodes* ticks. The three stages of Lyme disease are characterized by a bull's-eye rash, called erythema migrans (stage 1); joint, muscle, and nerve pain (stage 2); and arthritis with WBCs in the joint fluid (stage 3).
- **Ebola virus** spreads from human to human via body fluids and kills its victims quickly. Its viral proteins alter cytokine production and facilitate virus release from infected cells.

Glossary

septicemia
: An infection of the bloodstream.

viremia
: The presence of large numbers of virions in the bloodstream.

bacteremia
: A bacterial infection of the blood.

endocarditis
: An inflammation of the heart's inner lining.

bubonic plague
: A disease caused by the bacterium *Yersinia pestis* ; it is characterized by swollen lymph nodes that often turn black.

septicemic plague
: Infection of the bloodstream by *Yersinia pestis* .

pneumonic plague
: A highly virulent and contagious *Yersinia pestis* lung infection.

erythema migrans
: A bull's-eye rash characteristic of borreliosis (Lyme disease).

Lyme disease
: One form of borreliosis. A tick-borne disease caused by *Borrelia burgdorferi* , which may involve skin lesions and arthritis.

borreliosis
: Any of a variety of diseases caused by *Borrelia* species and transmitted by ticks or lice. Lyme disease is a form of borreliosis.

Fig. 20.39

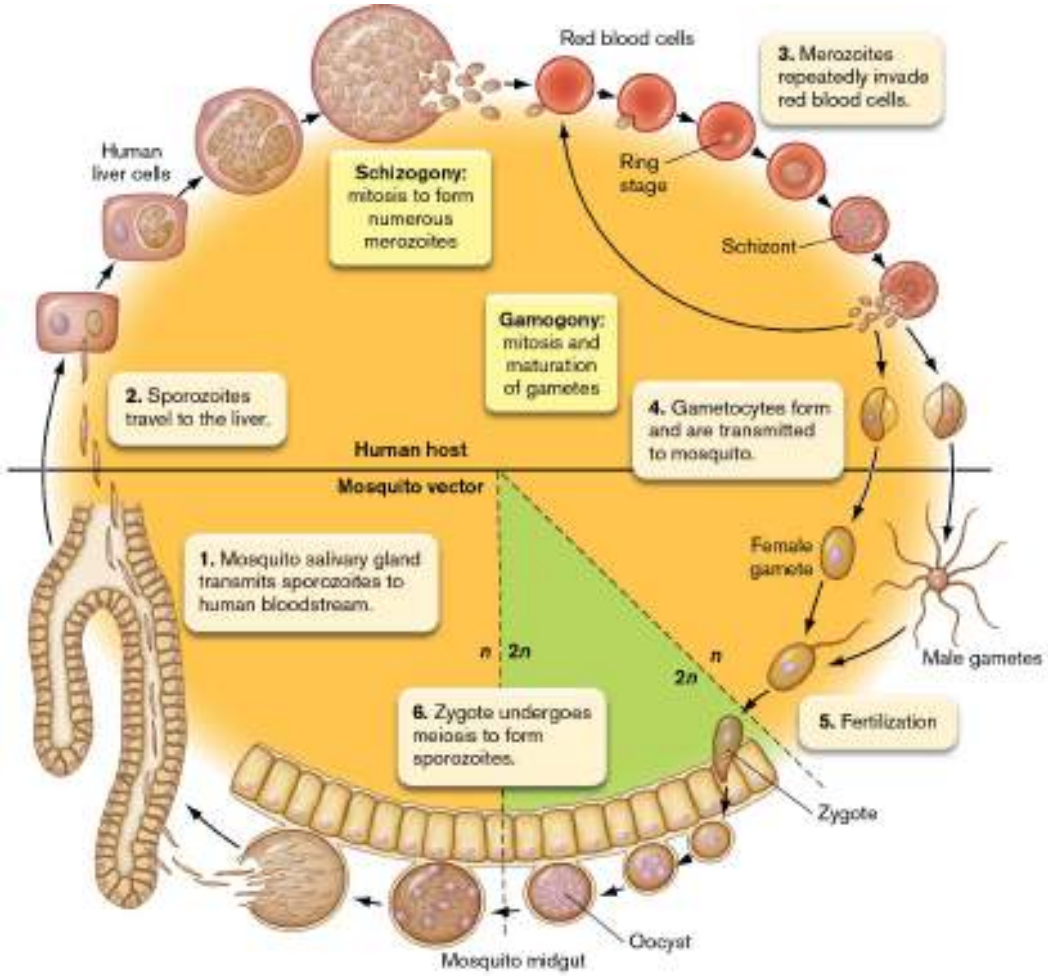


FIGURE 20.39 ■ Malaria: cycle of *Plasmodium falciparum* transmission between mosquito and human.

Fig. 20.39

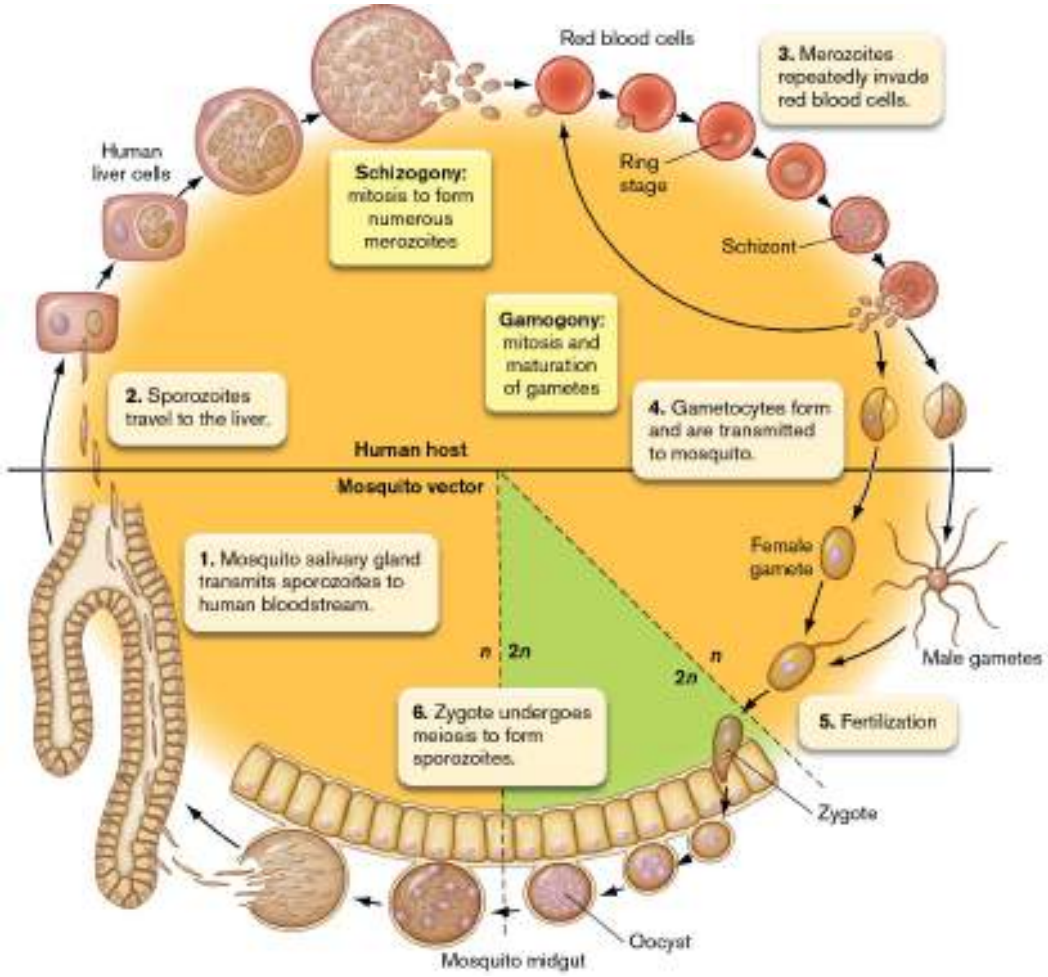


FIGURE 20.39 ■ Malaria: cycle of *Plasmodium falciparum* transmission between mosquito and human.

Fig. 25.4

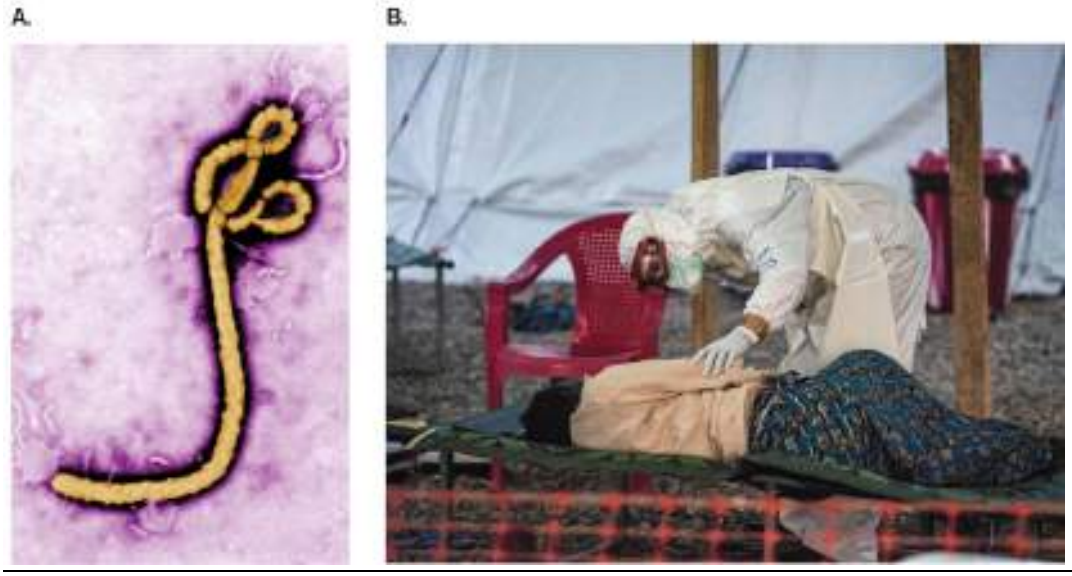


FIGURE 25.4 ■ Highly virulent viruses. A. Ebola virus (approx. 1 μm long; TEM). **B.** A health care worker tends to an Ebola patient in Kenema, Sierra Leone. Ebola causes hemorrhagic infections in which patients bleed from the mouth, nose, eyes, and other orifices. The mortality rate for this disease is approximately 50%.

CDC/FREDERICK A. MURPHY
TOMMY TRENCHARD/ALAMY STOCK PHOTO

Endnotes

1. Note a: G+ = Gram-positive; G− = Gram-negative. Return to reference a

26.6 Central Nervous System Infections

The brain and spinal cord are especially well protected against infection. Microbes cannot gain easy access to the brain, in large measure because of the blood-brain barrier , a filter mechanism that allows only selected substances into the brain. The blood-brain barrier works to our advantage when harmful substances, such as bacteria, are prohibited from entering. However, it works to our disadvantage when substances that we want to enter the brain, such as antibiotics, are kept out. The barrier is not a single structure but a function of the way blood vessels, especially capillaries, are organized in the brain. Furthermore, the endothelial cells in those vessels have tight junctions that do not allow most compounds or microbes to cross. And yet, brain infections do occur.

Case History: Meningitis

*Laila, a 4-month-old infant from Saudi Arabia, was hospitalized with fever, tender neck, and purplish spots (purpuric spots) on her trunk (**Fig. 26.36A**). Suspecting meningitis, the clinician took a cerebrospinal fluid (CSF) sample and examined it by Gram stain. The smear revealed Gram-negative diplococci inside PMNs. The CSF was turbid with 900 leukocytes per microliter, and* Neisseria meningitidis *was confirmed by culture. The child was treated with cefotaxime (a cephalosporin antibiotic; see Chapter 27) and made a full recovery. Her father, Abdul, the person who brought her in, was clinically well. However, the meningococcus was isolated from his oropharynx, as well as from the throat of the patient's 2-year-old brother. Isolates from the patient, her father, and her brother were positive by agglutination with meningococcal A/C/Y/W135 polyvalent reagent. Records showed that the father had previously received a quadrivalent meningococcal vaccine. All three isolates were confirmed to be meningococcus serogroup W135. DNA analysis found the three isolates to be indistinguishable, meaning that the father and his children were infected with the same strain of* N. meningitidis *. Why did Laila's brother not have meningitis? And why was Laila's vaccinated father colonized?*

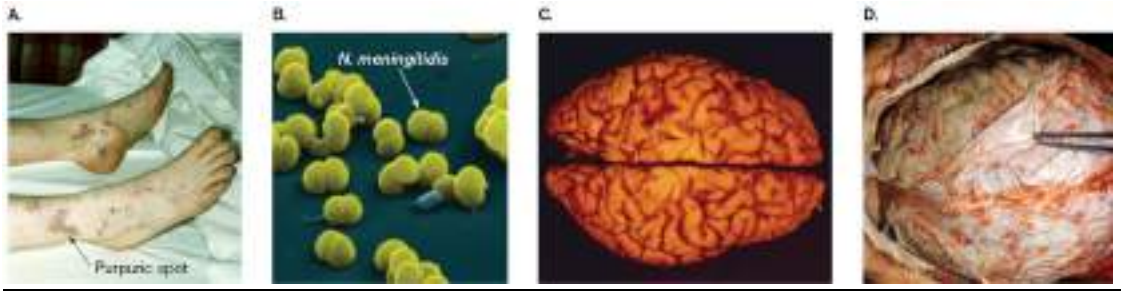


FIGURE 26.36 ■ Bacterial meningitis. A. Purpuric spots produced by local intravascular coagulation due to *Neisseria meningitidis* endotoxin. The rash in meningitis typically has petechial (small) and purpuric (large) components. **B.** *N. meningitidis* (diameter approx. 1 µm; SEM). **C.** Normal brain. **D.** Autopsy specimen of meningitis due to *Streptococcus pneumoniae* . Note the greening of the brain, compared with the pink normal brain.

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EYE OF SCIENCE/SCIENCE SOURCE
DR. COLIN CHUMBLEY/SCIENCE SOURCE
CDC

Meningitis is an inflammation of the meninges, the membranes that surround the brain and spinal cord. Meningitis can be either bacterial or viral in origin. Sinus and ear infections can extend directly to the meninges, whereas septicemic spread requires passage through the blood-brain barrier. Viral meningitis is serious but rarely fatal in people with a normal immune system. The symptoms generally persist for 7–10 days and then completely resolve. Bacterial meningitis is usually caused by *Streptococcus pneumoniae* , *Neisseria meningitidis* , or *Haemophilus influenzae* . Symptoms of bacterial meningitis can include sudden onset of fever, headache, pain or stiffness in the neck, painful sensitivity to strong light (photophobia), vomiting, and irritability. Prompt medical attention is extremely important because the disease can quickly progress to convulsions and death.

The meningococcus *N. meningitidis* (**Fig. 26.36B**) can colonize the human oropharynx, where it causes mild, if any, disease. At any given time, 10%–20% of the healthy population can be colonized and asymptomatic. The organism spreads directly by person-to-person contact or indirectly via droplet nuclei from sneezing or fomites. The problem arises when this organism enters the bloodstream. Unlike *N. gonorrhoeae* , the cause of gonorrhea, *N. meningitidis* is very resistant to complement, owing to its production of a polysaccharide capsule. Protected by this capsule, the microbe can produce a transient blood infection (bacteremia) and reach the blood-brain barrier.

How does *N. meningitidis* enter the bloodstream from the nasopharynx and then cross the blood-brain barrier? The organism initially uses type IV pili to adhere to and enter nasopharyngeal endothelial cells (type IV pili are discussed in Section 25.2). The bacteria then cross the endothelial cell layer by transcytosis , a process by which an internalized pathogen passes through a host cell along microtubules to the opposite side. Ultimately, the pathogen passes into the capillary lumen and is swept away to the brain. Once in the brain, type IV pili again adhere to endothelial cells, but this time they trigger the recruitment of host proteins that destabilize intercellular junctions. The bacteria then slip between the loosened junctions and enter the cerebrospinal fluid (CSF). Once in the CSF, microbes can multiply almost at will. **Figure 26.36C** and **D** shows the remarkable damage (greening) that *N. meningitidis* and other microbes, such as *S. pneumoniae* , cause in the brain.

Several antigenic types of capsules, called type-specific capsules, are produced by different strains of pathogenic *N. meningitidis* : types A, B, C, W135, and Y. Types A, C, Y, and W135 are usually associated with epidemic infections seen among people kept in close proximity, such as college students or military personnel. Type B meningococcus is typically involved in sporadic infections, but it has also been known to cause large outbreaks like the ones that occurred at Princeton University and UC Santa Barbara in 2013.

Antibodies to the capsular antigens are used to classify the capsular types of the organisms causing an outbreak. Knowing the capsular type of organism involved in each case helps determine whether the disease cases are related and where the infection may have started. In Abdul's case, a polyvalent reagent containing antibodies to the four main capsular types was used to confirm *N. meningitidis* , and antisera to individual capsule types specifically identified the strain as W135. Why was Abdul colonized but not ill? W135 likely colonized Abdul's throat but failed to spread because his previous vaccination provided circulating anti-W135 antibodies that attacked the organism if it entered the bloodstream. Even unvaccinated people can become colonized but remain asymptomatic if antibodies develop before the bacteria enter the bloodstream. He was protected.

Meningococcal meningitis is highly communicable. As a result, close contacts, such as the parents or siblings of any patient with meningococcal disease, should receive antimicrobial prophylaxis within 24 hours of diagnosis. Current recommendation is a single dose of ceftriaxone (a third-generation cephalosporin) for adults or 2 days of rifampicin for children. Highly susceptible populations can be immunized with a vaccine containing four of the five capsular

structures. Because the type B capsule is not immunogenic, a separate vaccine containing outer membrane vesicles and proteins from *N. meningitidis* type B (but not its capsule) is used.

Thought Question

26.11 Normal cerebrospinal fluid is usually low in protein and high in glucose. The protein and glucose content does not change much during a case of viral meningitis, but bacterial infection leads to greatly elevated protein and lowered glucose levels. What could account for this difference?

Case History: Botulism—It Is What You Eat

A 47-year-old resident of Oklahoma was admitted to the hospital with rapid onset of progressive dizziness, blurred vision, slurred speech, difficulty swallowing, and nausea. Findings on examination included drooping eyelids, facial paralysis, and impaired gag reflex. He developed breathing difficulties and required mechanical ventilation. The patient reported that during the 24 hours before the onset of symptoms, he had eaten home-canned green beans and a stew containing roast beef and potatoes. Analysis of the patient's stool detected botulinum type A toxin, but no Clostridium botulinum *organisms were found. The patient was hospitalized for 49 days, including 42 days on mechanical ventilation, before recovering and being discharged.*

Imagine a disease that causes complete loss of muscle function. Two microbes cause such lethal paralytic diseases by using secreted exotoxins (neurotoxins). In one instance, botulism, the victim suffers a flaccid paralysis in which the muscles go limp, as in the case history just presented, causing paralysis and respiratory difficulty. Botulism is typically a food-borne disease caused by an anaerobic, Gram-positive, spore-forming bacillus, named *Clostridium botulinum* , that produces botulism toxin.

In striking contrast to botulism is tetanus, a very painful disease in which muscles continually and involuntarily contract (called tetany or spastic paralysis). Tetanus is caused by tetanospasmin , a potent exotoxin made by another anaerobic, Gram-positive, spore-forming bacillus, called *Clostridium tetani* (**Fig. 26.37A**). Tetanospasmin alters neural transmission, but in contrast to botulism toxin (which inhibits neurotransmission), tetanospasmin causes excessive nerve signaling to muscles. The first symptom is usually spasms of the masseter muscles affecting movement of the jaw, giving the disease its common name—lockjaw. Eventually, the toxin forces the victim's back to arch grotesquely while the arms flex and legs extend (**Fig. 26.37B**). The patient remains locked this way until death. Spasms can even be strong enough to fracture the patient's vertebrae. In both botulism and tetanus, death can result from asphyxiation.

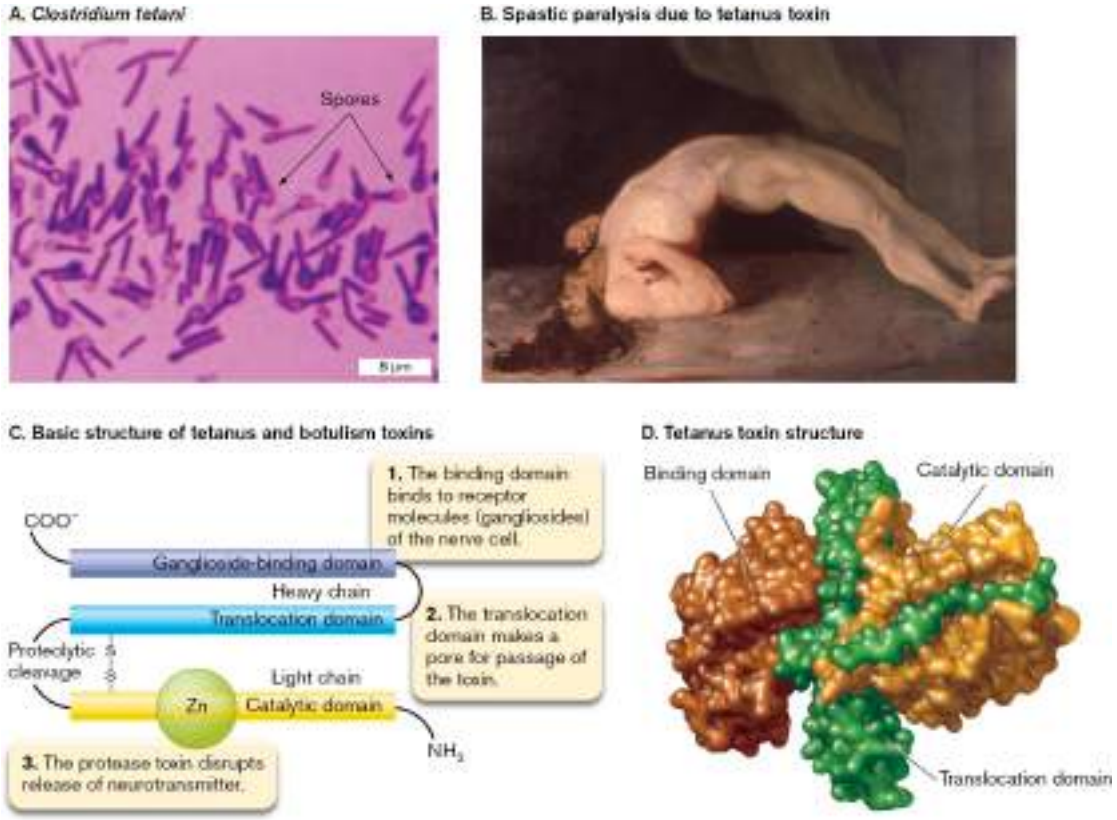


FIGURE 26.37 ■ Tetanus and botulism toxins. A. Photomicrograph of *Clostridium tetani* (cell length 4–8 μm). **B.** Painting from Charles Bell that depicts the spasms associated with tetanus in a soldier dying from tetanus. **C.** Schematic diagram of tetanus and botulism toxins. **D.** 3D representation of the tetanus neurotoxin, with the domains marked. (PDB code: 3BTA)

DR. A. M. SIEGELMAN/VISUALS UNLIMITED
THE PICTURE ART COLLECTION/ALAMY STOCK PHOTO

Thought Question

26.12 Given the symptoms of tetanus, what kind of therapy would you use to treat the disease?

Toxin structure and function. Botulism and tetanus toxins share 30%–40% identity. They have similar structures and nearly identical modes of action. Each is composed of two peptides—a large, or heavy, fragment analogous to a B subunit of AB toxins; and a small, or light, fragment analogous to an A subunit. Both toxins are initially made as single peptides (about 150 kDa) that are cleaved by host proteases after secretion to form two fragments (the heavy and light chains) that remain tethered to each other by a disulfide bond (**Fig. 26.37C**). The heavy chains possess binding domains for receptor molecules (gangliosides) on the nerve cell membrane and a translocation domain that makes a pore in the nerve cell endosome through which the toxic light

chains pass into the cytoplasm. The light chains are proteases that disrupt the movement of exocytic vesicles containing neurotransmitters (**Fig. 26.37D**).

Pathogenesis of botulism neurotoxin. Botulism is typically caused by ingesting preformed toxin. Rarely, infected wounds or ingested spores can also produce disease. Normally, spores germinate in contaminated food and the cells produce toxin, but an anaerobic environment is required because the organism is an anaerobe. Home-canning processes sterilize the food but also remove oxygen. If the sterilization is incomplete, surviving spores will germinate and the bacteria will secrete toxin. The toxin is heat sensitive but will remain active in improperly cooked food. After ingestion, the toxin is absorbed from the intestine. The organism is often absent from stool samples, but the toxin can be detected in stool.

A rare form of botulism, called infant botulism or "floppy head syndrome," can occur when infants (not older children) are fed honey. Honey can harbor *Clostridium botulinum* spores that can germinate in the gastrointestinal tract, after which the growing vegetative cells will secrete toxin.

Figure 26.38A and **B** illustrates normal neurotransmission at a neuromuscular junction. A signal sent from a motor neuron to the neuromuscular junction releases the neurotransmitter molecule acetylcholine (ACh) from vesicles in the axon terminal (**Fig. 26.38A**). **Figure 26.38B** shows the proteins that enable the vesicle and plasma membranes to fuse. Once released, ACh traverses the synapse and causes muscle contraction.

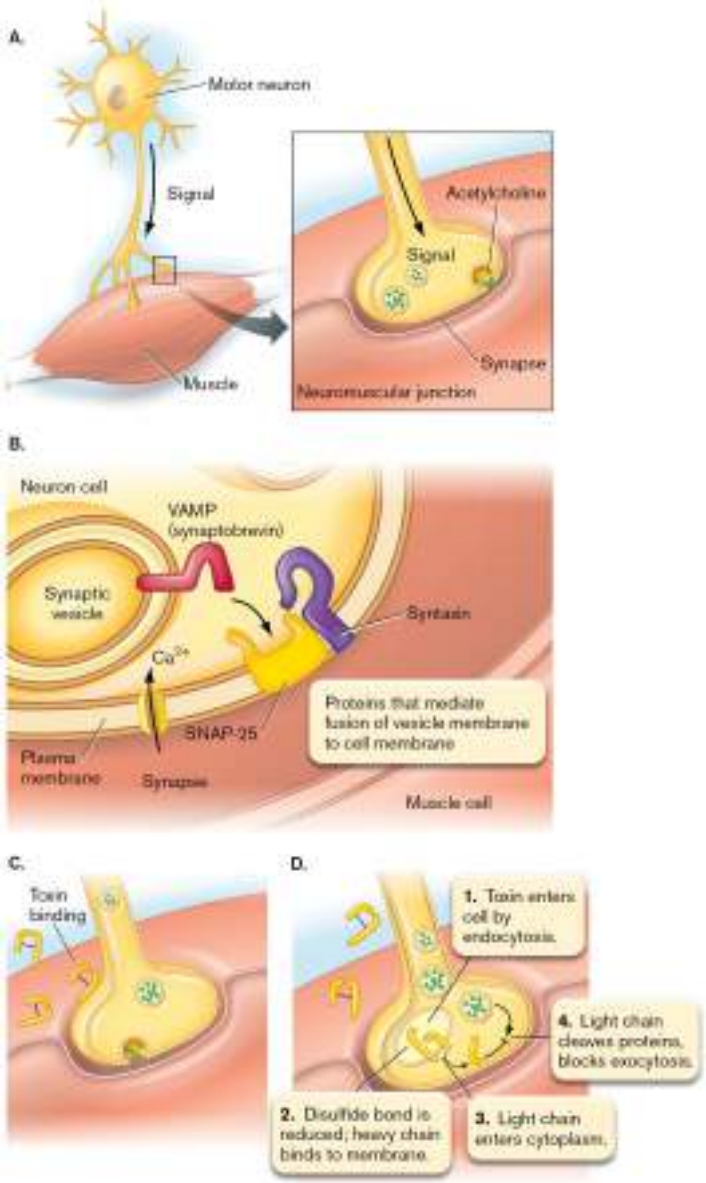


FIGURE 26.38 ■ Mechanism of action of botulism toxin. A. The neuromuscular junction. The blowup shows vesicles filled with neurotransmitters. **B.** A series of proteins within the nerve is needed to allow synaptic vesicles to bind to the nerve endings. Fusion of the membranes releases acetylcholine into the neuromuscular junction. Botulism toxin types A and E cleave SNAP-25. Botulism toxins B, D, F, and G cleave VAMP. Botulism toxin C1 cleaves syntaxin and SNAP-25. **C, D.** Toxin binds via the heavy chain and is endocytosed into the nerve terminal. Once the toxin cleaves its target, the nerve terminal is no longer able to release acetylcholine.

Botulism toxin enters a peripheral nerve by endocytosis (**Fig. 26.38C**), and acidification of the endosome reduces the disulfide bonds holding the heavy and light chains together. The heavy chain assembles as a channel in the endosome membrane through which the proteolytic light chain moves into the cytoplasm (**Fig. 26.38D**). The light chain then cleaves key host proteins, such as synaptobrevin (a vesicle-associated membrane protein, or VAMP), syntaxin, or

synaptosomal-associated protein (SNAP-25), involved in the exocytosis of vesicles containing acetylcholine. Without acetylcholine to activate nerve transmission, muscles will not contract and the patient is paralyzed. Currently, there is no FDA-approved vaccine for botulism. Treatment involves a multivalent antitoxin that can neutralize all seven toxin serotypes, coupled with supportive care.

Although botulism is now rare, the toxin is considered a select biological agent of potential use to bioterrorists. As such, its use in laboratories is under strict governmental control. But botulism toxin also has important medical uses. Because the toxin can safely relax muscles in a localized area if injected in small doses, botulism toxin, or Botox, is used therapeutically by neurologists to treat migraine headaches, excessive sweating, crossed eyes, and Bell's palsy. Most commonly, Botox is used cosmetically by plastic surgeons to reduce facial wrinkles.

Pathogenesis of tetanus neurotoxin. With such a high degree of structural and mechanistic similarity, why do tetanus and botulism toxins have such drastically different effects? The answer is based on where each toxin acts in the nervous system (**Fig. 26.39**). Tetanus, in contrast to botulism, is not a food-borne disease. *Clostridium tetani* spores are introduced into the body by trauma (such as by stepping on the wrong end of a nail). Necrotic tissue resulting from the puncture provides the anaerobic environment required for germination. Growing bacteria release tetanospasmin, which enters the peripheral nerve cells at the site of injury. But rather than cleaving targets here, the toxin travels up axons in the direction opposite to nerve signal transmission until it reaches the spinal column, where it becomes fixed at the presynaptic inhibitory motor neuron (**Fig. 26.39A**).

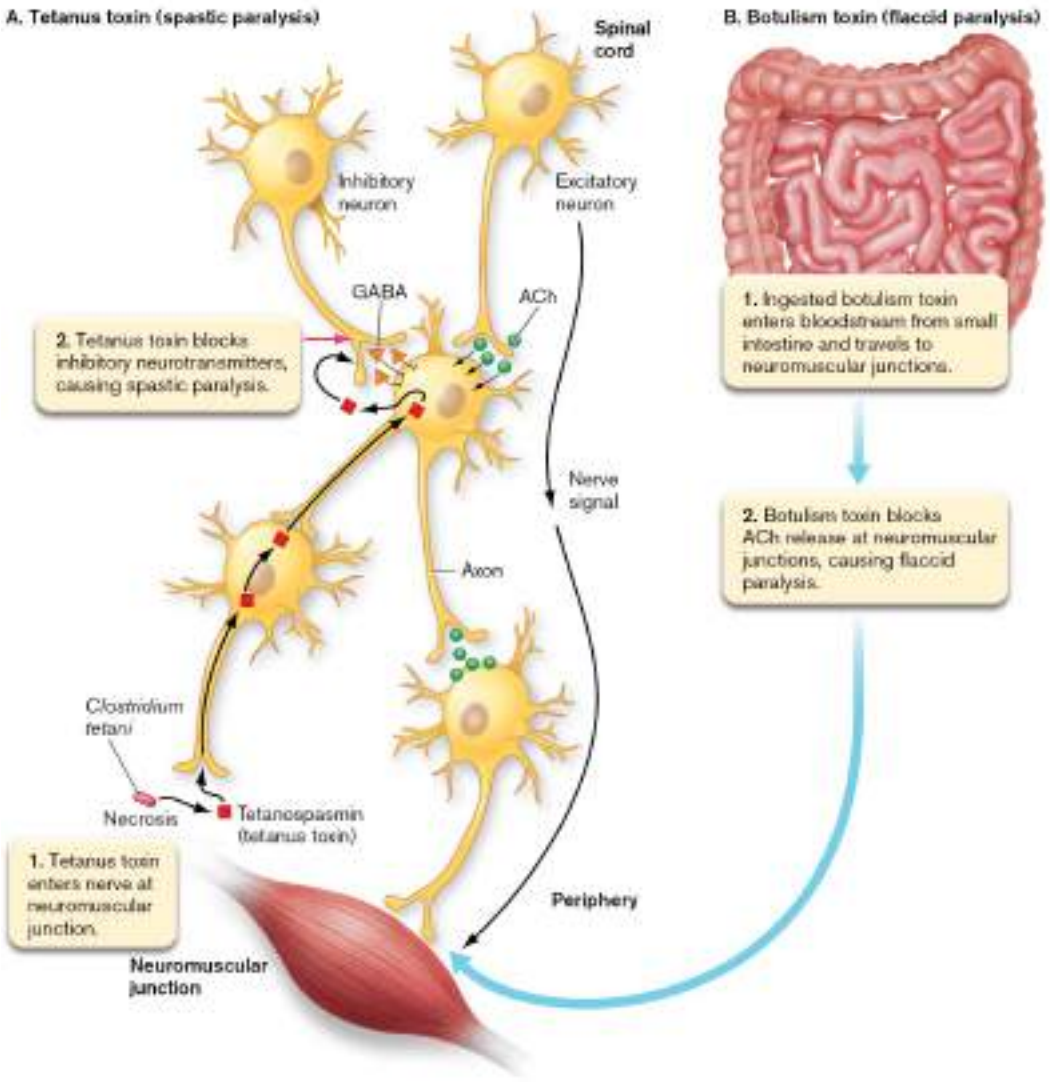


FIGURE 26.39 ■ Action of tetanus and botulism toxins. A. Tetanus toxin enters the nervous system at the neuromuscular junction (A1) and travels retrogradely up the axons until reaching an inhibitory neuron located in the central nervous system (A2). There it cleaves VAMP protein (Fig. 26.38B) associated with the exocytosis of vesicles containing inhibitory neurotransmitters (GABA). ACh = acetylcholine; GABA = gamma-aminobutyric (4-aminobutanoic acid). **B.** Botulism toxin is absorbed by the small intestine, enters the bloodstream, and acts at the neuromuscular junction to prevent release of acetylcholine.

There, the toxin also cleaves proteins like VAMP, but the vesicles in these nerves release inhibitory neurotransmitters (GABA and glycine) that dampen nerve impulses. Tetanus toxin blocks release of these inhibitors into the synaptic cleft, leaving nerve impulses unchecked. As a result, impulses come too frequently and produce the generalized muscle spasms characteristic of tetanus. A tetanus toxoid vaccine is available and is administered to children as part of the DTaP (diphtheria, tetanus, and acellular pertussis) vaccine (see Section 24.6).

Thought Questions

26.13 Figure 26.39 demonstrates that tetanus toxin has a mode of action (spastic paralysis) opposite to that of botulism toxin (flaccid paralysis). Since they have opposing modes of action, can botulism toxin be used to save a patient with tetanus?

Case History: Eastern Equine Encephalitis

In August, Mr. C took his 21-year-old son, Rich, to a New Jersey emergency department. Rich appeared dazed and had trouble responding to simple commands. When questioned about his son's activities over the previous few months, Mr. C told the physician that Rich had spent the month of July relaxing and sunning himself on New Jersey beaches and visiting a pond in a wooded area near a horse farm. On the afternoon prior to admission, Rich had become lethargic and tired. He returned home and went to bed. That evening, his father woke him for supper, but Rich was confused and had no appetite. By 11 p.m., Rich had a fever of 39.7°C (103.5°F) and could not respond to questions. A few hours later, when his father had trouble rousing him, he took Rich to the emergency department. Over the next week, Rich's condition worsened to the point where his limbs were paralyzed. Two weeks later, he died. Serum samples taken when he entered the hospital and a few days before he died showed a sixfold rise in antibody titer to eastern equine encephalitis (EEE) virus. Brain autopsy showed many small foci of necrosis in both the gray and white matter.

The EEE virus, a member of the family *Togaviridae* , is transmitted from bird to bird by mosquitoes. Horses contract the disease in the same way. Rich contracted it inadvertently while visiting the pond. Most people who are infected never develop symptoms, but among those who become ill, the disease is often fatal. The disease is rare, in part, because the species of mosquito that transmits the virus between marsh birds does not prey on humans. Occasionally, a human-specific mosquito will bite an infected bird and then transmit EEE virus to humans. Once in the human body, the virus generally does not fare well because the immune system thwarts viral replication.

An interesting point in the case history is that diagnosis relied on detecting an increase in antibody titer to the virus. Typically, at the point when disease symptoms first appear, the body has not had time to generate large amounts of specific antibodies. After a week or so, often when the patient is nearing recovery (convalescence), antibody titers have risen manyfold. The rule of thumb is that a greater-than-fourfold rise in IgG antibody titer between acute disease and convalescence (or, in this case, death) indicates that the patient has had the disease. While this knowledge could not help the patient in the case described here, it was valuable in terms of public health and prevention strategies.

EEE virus is one of many so-called arboviruses, a general term for pathogenic viruses transmitted to humans by arthropod insects. West Nile virus and yellow fever virus are two well-known arboviruses that cause CNS (central nervous system) infections. Additional bacterial, fungal, and viral causes of encephalitis and meningitis are listed in Table 26.7 .

TABLE 26.7	Selected Microbes That Cause Meningitis or Encephalitis				
Type of disease	**Etiological agent(s)** [a]	**Virulence factors**	**Typical initial infection or source**	**Treatment**	**Vaccine**
Bacterial (septic) meningitis	*Streptococcus pneumoniae* (G+)	Capsule, pneumolysin	Lung	Ampicillin	Multivalent, capsule
	Neisseria meningitidis (G−)	Capsule, IgA protease, endotoxin	Throat	Cephalosporin (3rd generation), ceftriaxone	Multivalent, capsule
	Haemophilus influenzae type b (G−)	Polyribitol capsule, IgA protease, endotoxin	Ear infection	Cephalosporin (3rd generation), ceftriaxone	Type b polysaccharide
	Other G− bacilli	Endotoxin	Septicemia		
	Group B streptococci (G+)	Sialic acid capsule, streptolysin, inhibition of alternate complement path	Neonate infected during parturition	Ampicillin	Capsular
	Listeria monocytogenes (G+)	Intracellular growth, PrfA regulator, actin-based motility	Mild GI disease of mother	Ampicillin plus gentamicin	

TABLE 26.7	Selected Microbes That Cause Meningitis or Encephalitis				
	Mycobacterium tuberculosis [e] (Gram-positive–like)	Cord factor, wax D, intracellular growth	Lung	Combination therapy (rifampin, isoniazid, ethambutol, pyrazinamide)	BCG [b]
	Staphylococcus aureus (G+)	Coagulase, protein A, TSST, leukocidin	Septicemia	Oxacillin, vancomycin	
	Staphylococcus epidermidis (G+)	Biofilm, slime	Complication of surgical procedure	Vancomycin, methicillin	
Aseptic meningitis [c]	Fungi (e.g., *Coccidioides* , *Cryptococcus*)		Sinusitis, direct spread to meninges	Ketoconazole, fluconazole	
	Amebas (e.g., *Naegleria*)		Swimming in contaminated waters	Amphotericin B	
	Treponema pallidum		Syphilis		
	Mycoplasmas	Adhesin tip	Respiratory	Erythromycin	
	Leptospira	Burrowing motility	Septicemia, water contaminated	Erythromycin	Killed whole cell, animals only

TABLE 26.7	Selected Microbes That Cause Meningitis or Encephalitis				
			with animal urine		
Viral meningitis or encephalitis	Viruses (90% caused by enteroviruses)			Self-limiting	
Eastern equine encephalitis	EEE virus	?	Mosquito bite	None; often fatal	
West Nile disease	West Nile virus	?	Mosquito bite	Supportive therapy [d]	

Prions Are Infectious Proteins

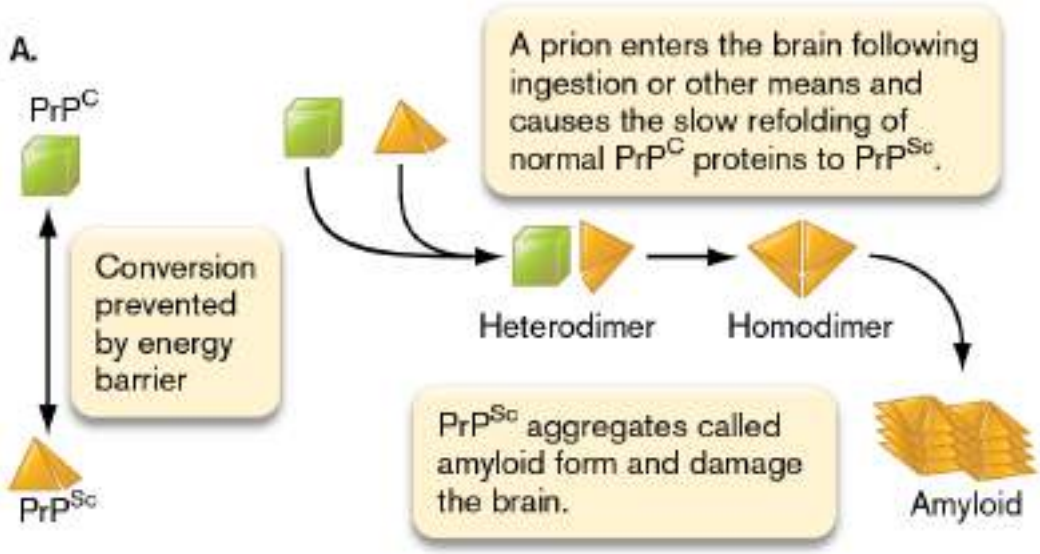
Imagine slowly losing your mind and knowing there is nothing you can do about it. An unusual infectious agent called the prion has been implicated as the cause of a series of relatively rare but invariably fatal brain diseases (Table 26.8). Prions are infectious agents that do not have a nucleic acid genome. The protein alone can mediate an infection. The prion is now recognized as an infectious, misfolded protein that resists inactivation by procedures that destroy proteins.

TABLE 26.8	Prion Diseases		
Disease	**Susceptible animal**	**Incubation period**	**Disease characteristics**
Creutzfeldt-Jakob [sporadic, familial, new variant (vCJD)]	Human	Months (vCJD) to years	Spongiform encephalopathy (degenerative brain disease)

TABLE 26.8	**Prion Diseases**		
Kuru	Human	Months to years	Spongiform encephalopathy
Gerstmann-Straussler-Scheinker syndrome	Human	Months to years	Genetic neurodegenerative disease
Fatal familial insomnia	Human	Months to years	Genetic neurodegenerative disease with untreatable insomnia
Mad cow disease	Cattle	5 years	Spongiform encephalopathy
Wasting disease	Deer	Months to years	Spongiform encephalopathy

The discovery that proteins alone can transmit an infectious disease came as a surprise to the scientific community. Diseases caused by prions are especially worrying, since prions resist destruction by many chemical agents and remain active after heating at extremely high temperatures. There have even been documented cases in which sterilized neurosurgical instruments, originally used on a prion-infected person, still held infectious agent and transmitted the disease to a subsequent surgical patient. Extremely rigorous decontamination procedures, such as autoclaving surgical instruments immersed in 1-M sodium hydroxide, will destroy prions.

How can a nonliving entity without nucleic acid be an infectious agent? Prions associated with human brain disease are thought to be aberrantly folded forms of a normal brain protein (PrP^{C}). The theory is that when a disease-related prion, designated PrP^{Sc} or PrP^{D}, is introduced into the body and manages to enter the brain, it will cause normally folded forms of the protein to refold incorrectly (**Fig. 26.40A**). The improperly folded proteins fit together like Lego blocks to produce damaging aggregated structures within brain cells.



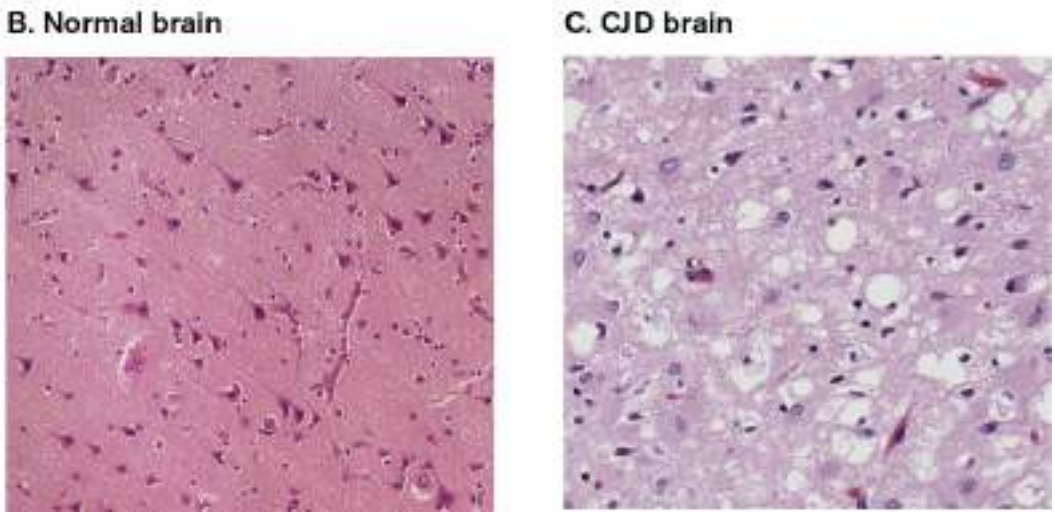


FIGURE 26.40 ■ Spongiform encephalopathies. A. Refolding model of prion diseases. PrP is a brain protein that can take two forms: the normal form (PrP^{C}), which is a natural brain protein; and the prion form (PrP^{Sc}). **B.** Normal brain section. **C.** Section of brain taken from a CJD victim. Note the Swiss-cheese appearance, indicating brain damage.

SCIENCE STOCK PHOTOGRAPHEY/SCIENCE SOURCE
CDC/TERESA HAMMETT

Prion diseases are often called spongiform encephalopathies because the postmortem appearance of the brain includes large, spongy vacuoles in the cortex and cerebellum. These are visible in a brain sample from a victim of one of these diseases, called Creutzfeldt-Jakob disease (CJD; **Fig. 26.40C**). Most mammalian species appear to be susceptible to these diseases.

Since 1996, mounting evidence has pointed to a causal relationship between outbreaks in Europe of a disease in cattle called bovine spongiform encephalopathy (BSE, or "mad cow

disease"), which is caused by prions, and a disease in humans called variant Creutzfeldt-Jakob disease (vCJD). Both disorders are invariably fatal. For humans to contract disease, prions from contaminated meat are ingested and penetrate the intestinal mucosa via the antigen-sampling M cells in Peyer's patches. The circulation then traffics the agent to the brain.

Between 1993 and 2018, only six cases of BSE in cattle were detected in the United States. Because of aggressive surveillance efforts in the United States and Canada (where 20 cases have been found since 1993), it is unlikely, but not impossible, that BSE will be a food-borne hazard to humans in both countries. The CDC monitors the trends and current incidence of typical CJD (approximately 560 cases in 2019) and variant CJD (4 cases total) in the United States. The worldwide incidence of CJD is one per 1 million population.

There is no cure for CJD or vCJD. Two tests to detect PrP^{Sc} in asymptomatic primates, including humans, have been developed and are being used for human screening. One test is called protein-mediated cyclic amplification (PMCA). The other is called the real-time, quaking-induced conversion (RT-QuIC) assay. PMCA has successfully identified the presence of very tiny amounts of PrP^{Sc} in CSF, blood, or urine. RT-QuIC performs best for CSF. The PMCA process involves adding large amounts of normal PrP (PrP^{C}) to samples containing tiny amounts of PrP^{Sc} prions. The prions, if present in the sample, will seed the misfolding of PrP^{C} to PrP^{Sc} molecules that aggregate. Sonication is then used to partially break up the newly formed PrP^{Sc} aggregates into pieces that can further seed the misfolding and aggregation of normal PrP. Repeated cycles of sonication-incubation will exponentially amplify the amount of PrP^{Sc} present in a sample. The PrP^{Sc} is then identified by western blot. RT-QuIC is similar, except it uses a recombinant PrPc and shaking instead of sonication. Both tests have been used clinically since 2015 to diagnose CJD as probable.

In this chapter we describe key concepts of infectious disease using just a small sample of disease-causing pathogens. Other diseases are considered elsewhere in the book. In the next chapter we describe how humans fight back against pathogens using pharmacology to sabotage the physiology of the infecting microbes.

To Summarize

- ***Neisseria meningitidis*** is resistant to serum complement because it produces a type-specific capsule that enables the organism to reach and then cross the blood-brain barrier.
- In contrast to *Neisseria gonorrhoeae* , a **vaccine for *N. meningitidis* is available** .
- **Botulism toxin** causes flaccid paralysis.
- **Tetanospasmin** causes spastic paralysis.
- **Serological diagnosis of many infectious diseases** is possible if the specific pathogen IgG antibody titer rises fourfold between the acute and convalescent stages of disease (eastern equine encephalitis virus, for instance).
- **Spongiform encephalopathies** are believed to be caused by nonliving proteins called prions.

Glossary

blood-brain barrier
: A selectively permeable membrane made up of tightly packed capillaries that supply blood to the brain and spinal cord. Large molecules and most pathogens cannot permeate the narrow

spaces. Fat-soluble (lipophilic) molecules and oxygen can dissolve through the capillary cell membranes and are absorbed into the brain.

transcytosis
: The movement of a cell or substance from one side of a polarized cell to the other side, using an intracellular route.

botulism
: A food-borne disease caused by a *Clostridium botulinum* toxin, involving muscle paralysis.

tetanospasmin
: The tetanus-causing potent exotoxin produced by *Clostridium tetani* .

prion
: An infectious agent that causes propagation of misfolded host proteins; usually consists of a defective version of the host protein.

spongiform encephalopathy
: A brain-wasting disease caused by a prion.

Endnotes

1. Note a: G+ = Gram-positive; G− = Gram-negative. Return to reference a
2. Note b: BCG = Bacille Calmette-Guérin (a weakened strain of the bovine tuberculosis strain). Return to reference b
3. Note c: For aseptic meningitis, bacterial sources cannot be isolated by ordinary means. Return to reference c
4. Note d: Supportive therapy = hospitalization, intravenous fluids, airway management, respiratory support, and prevention of secondary infections. Return to reference d
5. Note e: Mycobacteria do not stain by Gram stain, but they have a wall structure similar to Gram-positive bacteria. Return to reference e

eResearch Activity 26

Can a Microbiome "Learn" from an Infection?

Human survival depends on a diverse microbiome that provides numerous advantages (see Section 23.1). One of the advantages is to stymie colonization by pathogens. The process is especially evident in the gut, where competition for mucosal binding sites and secretion of antimicrobials by native microbiota make colonization by bacterial pathogens difficult. However, Apollo Stacy and Yasmine Belkaid at the National Institutes of Health have wondered whether surviving an infection can actually "train" the host microbiome to be even more vigilant in preventing a future infection.

The scientists and their colleagues used several types of mice to test their hypothesis, but they mostly relied on two. They used germ-free mice completely lacking microbiota, gut or otherwise, and they also used specific pathogen–free (SPF) mice, which have a microbiome known to lack specific pathogens. Because SPF mice are maintained and bred in a controlled laboratory environment, their microbiomes differ from those of wild-type mice that have experienced pathogens.

To train the microbiomes of SPF mice, an attenuated strain of *Yersinia pseudotuberculosis* with a deletion in the virulence gene *yopM* (designated Δ *yopM Yptb*) was orally administered to SPF mice. Inflammation developed in the mouse gut, but the infection cleared within a couple of days. After the infection cleared, the scientists used fecal microbiome transplantation (FMT) techniques to introduce the Δ *yopM Yptb* - trained microbiome into germ-free mice. The control population was comprised of germ-free mice transplanted with the untrained microbiome of uninfected SPF mice (**Fig. ERA 26.1**).

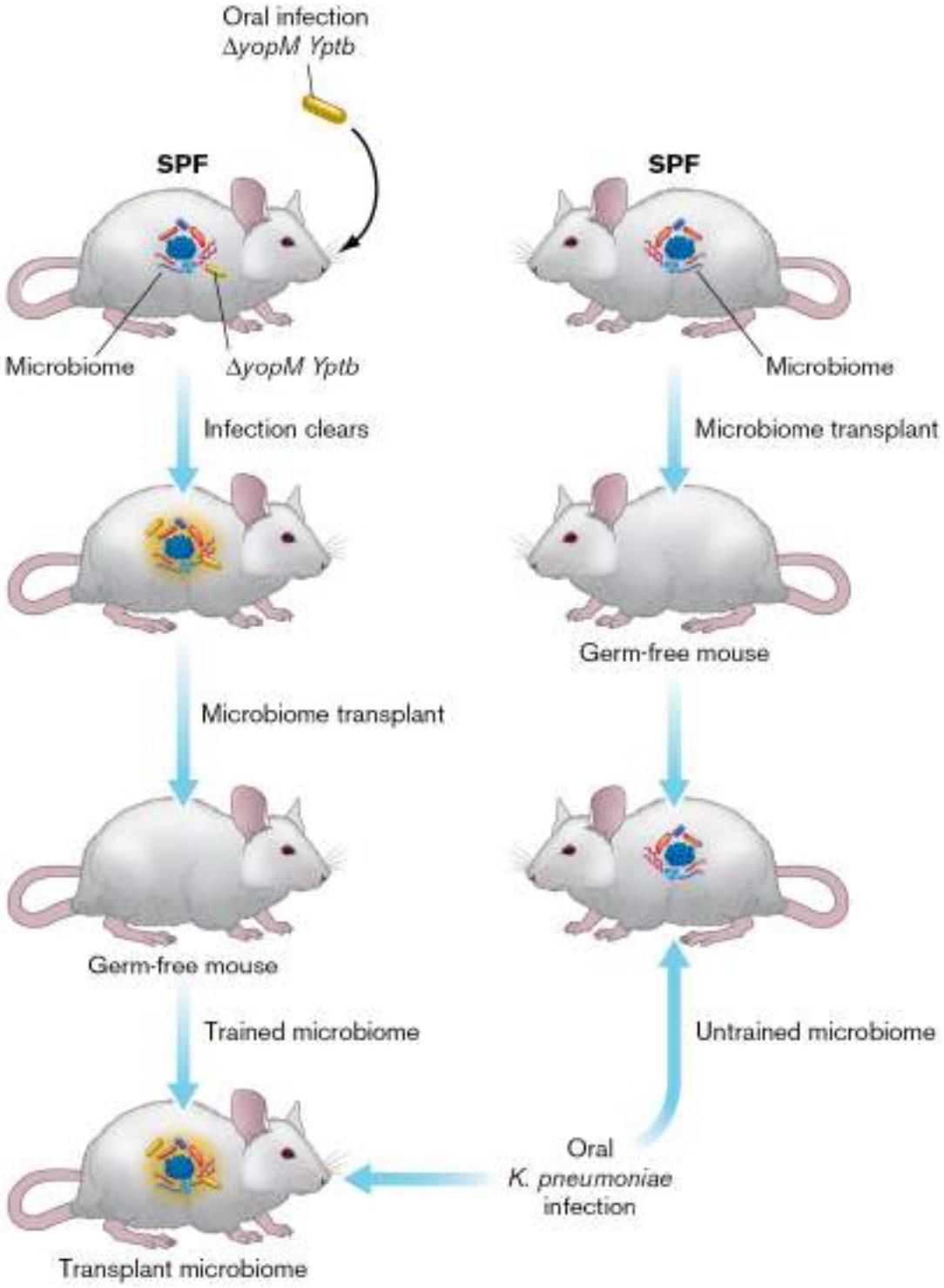


FIGURE ERA 26.1 ■ Strategy for training the microbiome. SPF mice were orally infected with the attenuated Δ *yopM Yersinia pseudotuberculosis* (*Yptb*). After the infection

cleared (2 days), the trained microbiome was transplanted to a germ-free mouse. At the same time, an untrained microbiome from an uninfected SPF mouse was transplanted to another germ-free mouse. Both transplanted-germ-free mice were then orally infected with *Klebsiella pneumoniae* . Four weeks later, feces were assayed for colony-forming units of *K. pneumoniae.*

In early experiments, the authors orally infected both sets of FMT mice with the hospital-associated pathogen *Klebsiella pneumoniae* (*Kpn*) carrying chloramphenicol resistance. One day later, they compared *Kpn* numbers (CFUs) in the feces of both sets as a measure of colonization (**Fig. ERA 26.2**). The results showed that the trained microbiota from postinfection Δ *yopM Yptb* mice conferred resistance to *Kpn* colonization.

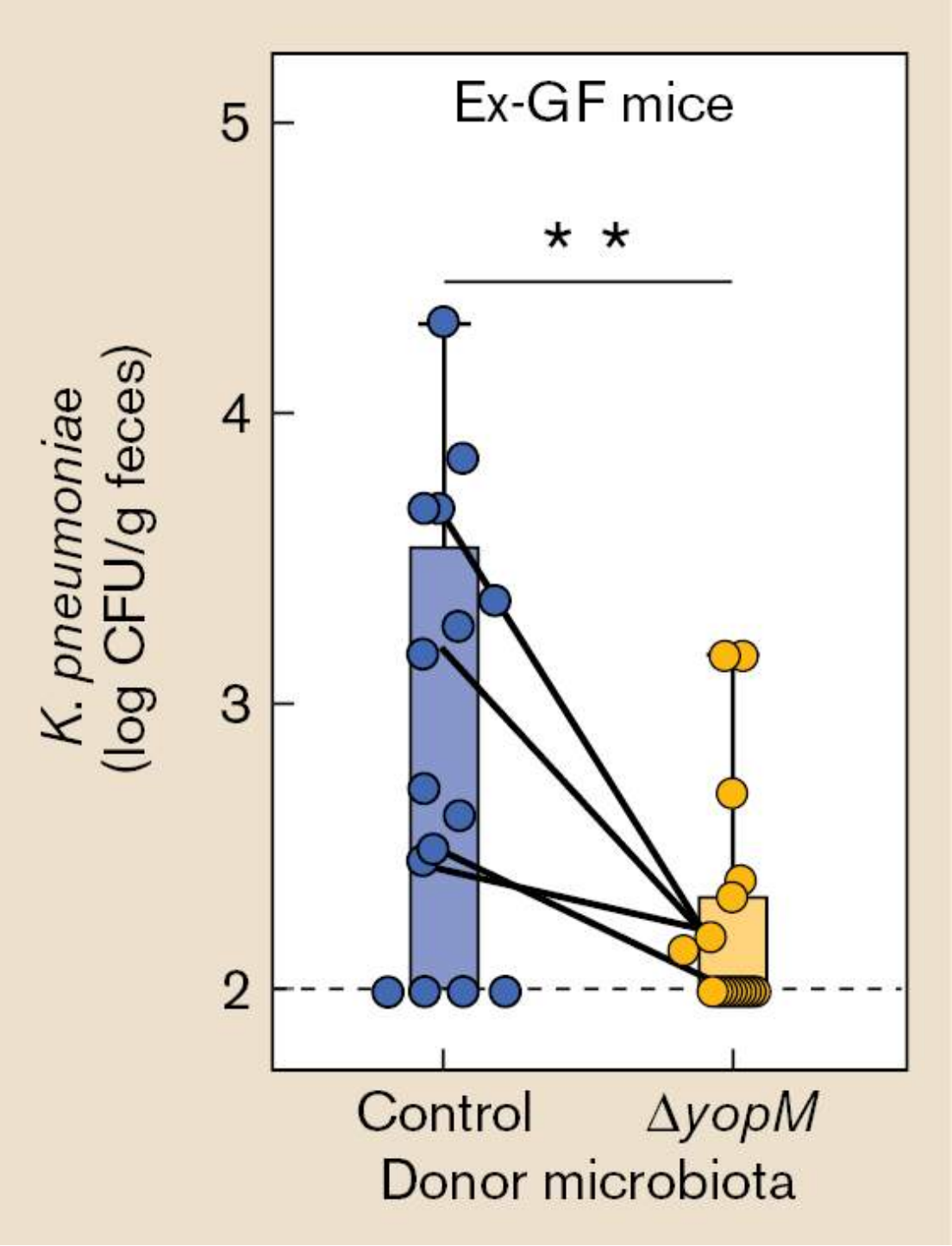


FIGURE ERA 26.2 ■ Infection-trained microbiota enhance resistance to Kpn colonization. Controls (ctrl) are germ-free mice transplanted with SPF microbiota. Δ *yopM* are germ-free mice transplanted with microbiota from Δ *yopM Yptb* -infected SPF mice. Data points (*y* -axis) represent CFUs of *Kpn*

(chloramphenicol resistant) bacteria found per gram of feces per mouse one day after *Kpn* infection. ** $p < 0.01$. Each dot represents a different mouse.

After comparing the 16S ribosomal RNA profiles of microbiota from the post-Δ *yopM Yptb*- infected SPF mice to profiles of microbiota from uninfected SPF mice, the authors discovered that the most reproducibly enriched class in the trained microbiome were the Deltaproteobacteria (recently renamed Myxococcata). Shotgun metagenomes of microbiota from the post-Δ *yopM Yptb*- infected mice revealed that six enriched metabolic functions could be assigned to sulfur metabolism and menaquinone biosynthesis. A key feature of Deltaproteobacteria is that species in that class can collaborate with species from other phyla to respire anaerobically using sulfur-containing compounds such as taurine or sulfate. *Desulfovibrio* species, for instance, can convert taurine to sulfite via taurine-pyruvate aminotransferase (encoded by *tpa*). *Bacteroides* species can transform sulfate to sulfite using sulfate adenylyltransferase (*sat*). Then *Desulfovibrio* species can transform the sulfite to sulfide by dissimilatory sulfite reductase (*dsr*) using electrons donated by menaquinone (**Fig. ERA 26.3A**).

The authors next found that the abundance of *tpa* genes (from *Desulfovibrio*) was about 4 times that of *sat* (from *Bacteroides*) in the Δ *yopM Yptb* -trained microbiome, suggesting that taurine rather than sulfate was responsible for the expansion of Deltaproteobacteria. Indeed, mass spectrometry confirmed that taurine was the most significantly increased metabolite in the cecum of post-Δ *yopM Yptb*- infected mice, even 15 weeks after infection (**Fig. ERA 26.3B**). The source of this taurine appeared to be increased production of taurine-conjugated bile acids in the livers of post-Δ *yopM Yptb* -infected mice.

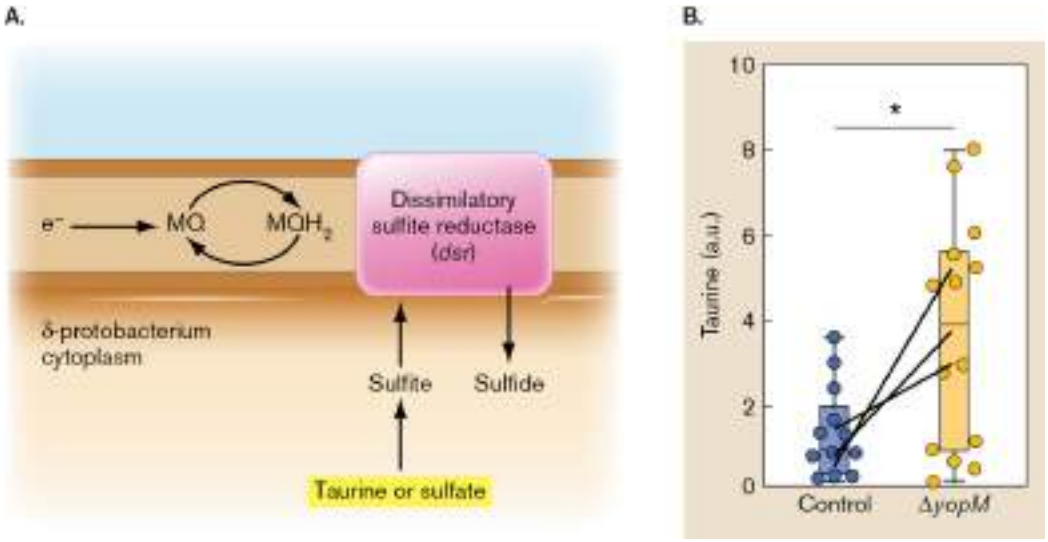


FIGURE ERA 26.3 ■ The expansion of Deltaproteobacteria during infection correlates to increased taurine levels in the gut. A. Model for Deltaproteobacteria energy generation. MQ = oxidized menaquinone; MQH_2 = reduced menaquinone. **B.** Abundance of taurine in the fecal contents of control and post-Δ *yopM Yptb* mice at >15 weeks post-Δ *yopM Yptb* infection.

The authors then wondered if adding taurine alone to germ-free mice devoid of microbiota would provide resistance to *Kpn* colonization. It did not. However, transplanting microbiota harvested from taurine-treated SPF mice to germ-free mice did promote resistance to *Kpn* (**Fig. ERA 26.4A**).

A major by-product of taurine metabolism resulting from the activity of Dsr (sulfite reductase), an enzyme mentioned earlier (**Fig. ERA 26.3A**), is the poisonous gas hydrogen sulfide (H_2S). H_2S at high doses can poison cytochrome oxidases used in aerobic electron transport chains to generate usable energy. The metagenomic data suggested that taurine-trained microbiota would produce more H_2S than the control microbiota. **Figure ERA 26.4B** illustrates that taurine-trained microbiota produced significantly

more H_2S when grown in taurine medium than did control microbiota.

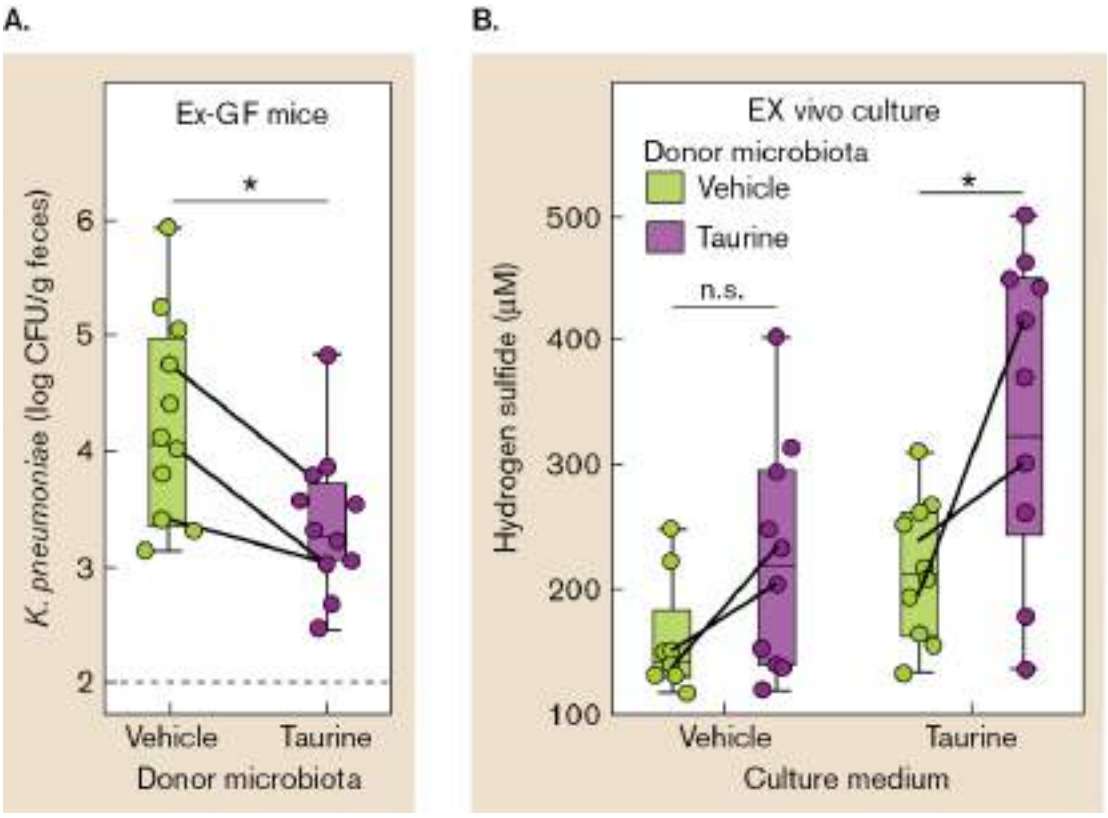


FIGURE ERA 26.4 ■ Taurine-trained microbiota enhance colonization resistance and hydrogen sulfide production. **A.** *Kpn* in the feces of ex-germ-free (Ex-GF) mice that were transplanted with microbiota from vehicle-treated or taurine-treated SPF mice. Counts were determined one-day after *Kpn* infection. veh = vehicle. **B.** Ex vivo generation of H_2S by microbiota taken from vehicle-treated SPF mice (green bars) and taurine-treated SPF mice (purple bars) grown in culture medium without taurine (+veh) or with taurine (+taurine).

The authors then proposed a model that pathogens equipped with cytochrome oxidases can use oxygen as a terminal electron acceptor to metabolize and grow on nonfermentable substrates as long as taurine levels are low. However, at high levels of taurine,

taurine-derived H_2S would inhibit the cytochrome oxidases and prevent pathogens from using these substrates.

By screening transposon mutants in *K. pneumoniae* , the team discovered that the metabolism of 1,2-propanediol, a nonfermentable substrate, was required to bolster *Kpn* fitness (colonization) in control SPF mice (low taurine) but had no effect on colonization in post-Δ *yopM Yptb* -infected mice (high taurine). *Kpn* can metabolize 1,2-propanediol only in the presence of oxygen. Consistent with their model, **Figure ERA 26.5** illustrates that sodium hydrosulfide prevented *Kpn* from growing in vitro on 1,2-propanediol under aerobic conditions, whereas the precursors to sulfide such as taurine and taurocholate (a taurine-conjugated bile acid) were not inhibitory, indicating the precursors must be converted to sulfide to be effective.

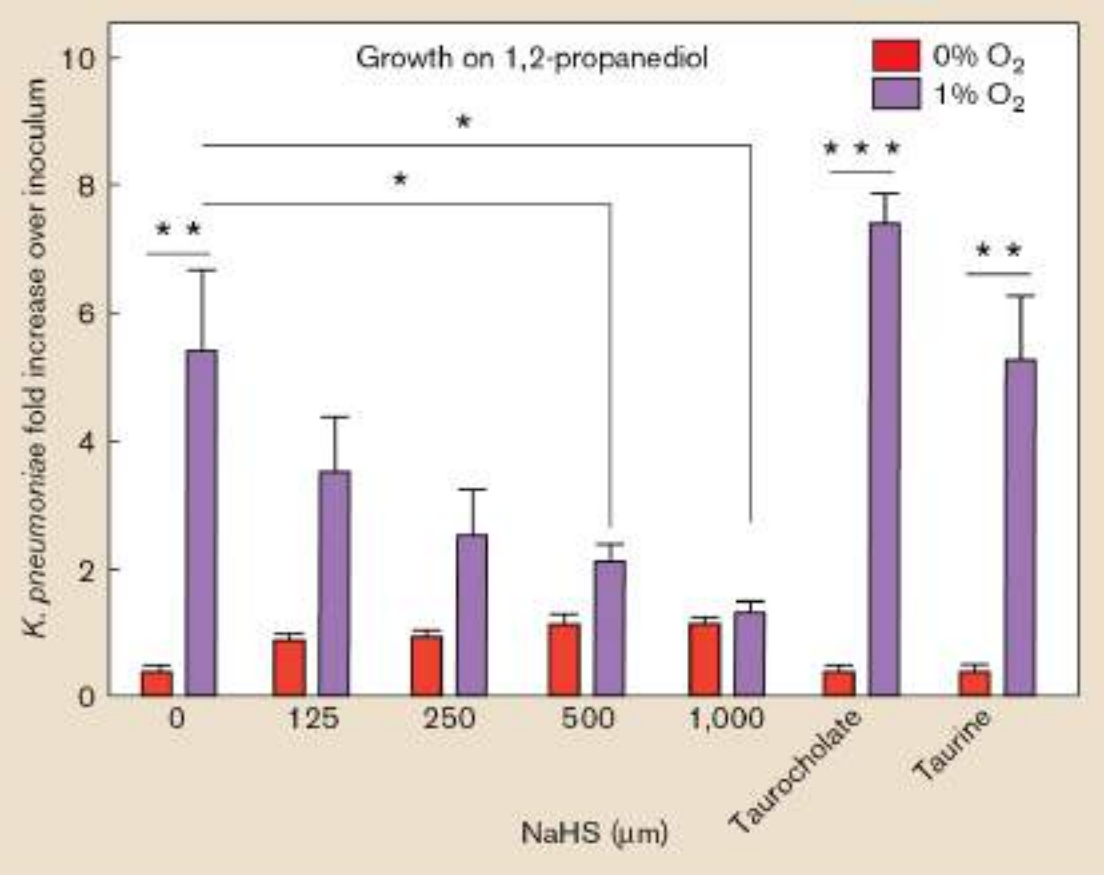


FIGURE ERA 26.5 ■ Sulfide added in vitro prevents aerobic growth of *Kpn* on 1,2-propanediol. Taurocholate (5

mM) and taurine (5 mM) precursors of sulfide did not affect growth on 1,2-propanediol.

The authors conclude that transient infection can establish long-term "metaorganism memory." The model is summarized in **Figure ERA 26.6** . Metaorganism memory relies on interdependent host and microbiome functions. In this case, the host responds to infection by increasing the production of bile acids. Some members of the microbiome, in turn, convert a bile acid metabolite (taurine) to the antimicrobial sulfide. Sulfide interferes with bacterial cytochrome oxidases, the consequence of which is to change microbiome composition and inhibit the growth of potentially pathogenic bacteria present in low numbers.

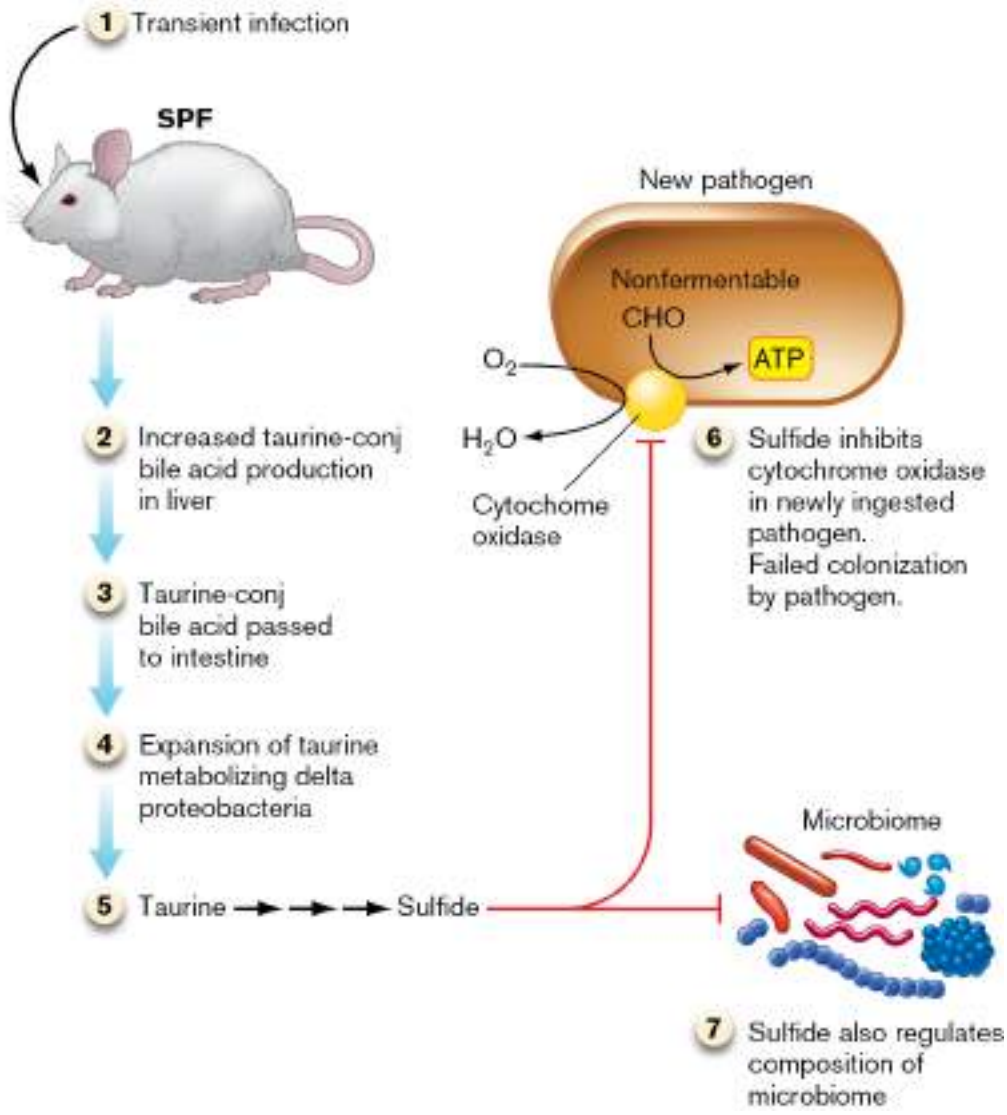


FIGURE ERA 26.6 ■ Model of metaorganism memory. A transient infection triggers host responses, including metabolites, that the microbiota use to alter their own composition and limit growth of newly introduced pathogens. In this model, sulfide produced from microbial metabolism of host-made taurine will poison a bacterial cytochrome oxidase needed by potential bacterial pathogens (step 6) and by certain members of the microbiome to aerobically metabolize nonfermentable carbohydrates.

Note that some of these metabolites can also affect immune system memory and stimulate synthesis of antimicrobial peptides. The results of this paper, therefore, suggest that the immune system works in concert with the microbiome to promote colonization resistance against infection. So, the answer to our opening question is that a microbiome can "learn" from an infection! This innovative study was funded by numerous agencies, including the National Institutes of Health, the PEW Latin American Fellows Program, and Human Frontier Science Program.

Further Exploration

Design an experiment using bismuth, a compound that sequesters sulfide, to determine if the composition of resident microbiota will be altered by sulfide in the absence of infection. You can assume that there is a basal level of H_2S produced even in the absence of an infection.

Apollo Stacy, Vinicius Andrade-Oliveira, John A. McCulloch, Benedikt Hild, and Ji Hoon Oh. 2021. Infection trains the host for microbiota-enhanced resistance to pathogens. *Cell* **184** :615–627. https://doi.org/10.1016/j.cell.2020.12.011

CHAPTER REVIEW

Review Questions

1. Organize a list of pathogens by their mechanism of transmission (fecal-oral, aerosol, and so on).
2. Discuss some common skin infections.
3. What causes boils?
4. What are the symptoms of necrotizing fasciitis?
5. What is the difference between primary and secondary infections?
6. How do pneumococci avoid engulfment by phagocytes?
7. What causes the clouding seen in X-rays of infected lungs?
8. What are the key features of the pneumococcal vaccine?
9. Name the common fungal causes of lung disease.
10. What is the clinical course of COVID-19 disease?
11. What is the Ghon complex, and what distinguishes primary from secondary tuberculosis?
12. Why is diarrhea watery?
13. What is the most common microbial cause of diarrhea?
14. List common bacterial agents that cause diarrhea.
15. Would you suspect *Salmonella* infection in a cluster of nauseated patients rushed to the hospital directly from a church picnic? Why or why not?
16. What is the significance of finding leukocytes in stool?

17. What is one reservoir of *E. coli* O157:H7?

18. How is a UTI diagnosed?

19. What is an important virulence determinant of uropathogenic *E. coli* ?

20. What is the most common sexually transmitted infection?

21. How is gonorrhea different in men and women?

22. Why will *Neisseria gonorrhoeae* not usually disseminate in the bloodstream, while *N. meningitidis* will?

23. Name the major causes of bacterial meningitis. What are the two routes of infection?

24. If tetanus and botulism toxins have the same mode of action, why do they cause opposite effects on muscles?

25. What are some virulence factors of *Yersinia pestis* ?

26. Members of one class of infectious agent cannot be treated with antimicrobial chemotherapy. Explain why.

Thought Questions

1. Chickenpox is a disease of children and young adults caused by herpesvirus 3 (varicella). It is characterized by a rash of fluid-filled vesicles that eventually become crusty. The rash starts on the trunk and spreads to the extremities. Illness usually resolves in 7–10 days, and the patient becomes immune to the disease. However, some individuals later in life (usually over age 50) develop a painful disease, called shingles, that is caused by the same virus—even if they have never been reexposed to the virus. The lesions are tender, persistent vesicles that form on the skin. Propose a plausible explanation, considering the age of the shingles victims and the

occurrence of severe pain in this illness, for how they contracted shingles and why the lesions are painful.

2. A 5-year-old boy was brought to the emergency room by his grandmother, who had found him on the floor of her apartment covered in bloody, loose feces. Patient history revealed that the boy attended day care regularly. The diagnostic laboratory determined the etiological agent to be a Gram-negative rod. This organism is a facultative intracellular pathogen that escapes the host cell vacuole and moves in and between cells by actin polymerization. From your reading of Chapters 25 and 26 , what do you think are the most likely genus and species involved in this case? Why is the fact that the boy attended day care significant?
3. Why are urinary tract infections among the most commonly acquired nosocomial (hospital-acquired) infections?
4. On the Internet, find the MMWR (Morbidity and Mortality Weekly Report) that provides the "notifiable infectious diseases" weekly tables (the URL for data as of this writing is http://wonder.cdc.gov/nndss/nndss_weekly_tables_menu.asp). Study the tables that summarize the weekly incidence of gonorrhea and West Nile disease. For the latter, you may need to view one of the arboviral tables to find "West Nile virus disease" or "WNV disease." Explain the differences in the weekly incidence of these two diseases, and then view the incidence of those diseases in your state.
5. Why do new versions of swine and avian flu often originate in Asia?

Key Terms

- bacteremia (1142)
- blood-brain barrier (1154)
- borreliosis (1151)
- botulism (1156)
- bubonic plague (1148)
- cellulitis (1107)
- chancre (1135)
- chlamydia (1136)
- congenital syphilis (1136)
- cystitis (1132)
- differential (1103)
- empiric therapy (1106)
- endocarditis (1142)
- erythema migrans (1150)
- granuloma (1115)
- health care–associated infection (HAI) (1105)
- hepatitis (1128)
- hepatitis A virus (HAV) (1129)
- hepatitis B virus (HBV) (1129)
- hepatitis C virus (HCV) (1130)
- Lyme disease (1150)
- multisystem inflammatory syndrome in children (MIS-C) (1117)
- necrotizing fasciitis (1106)
- norovirus (1123)
- nosocomial (1105)
- pneumonic plague (1148)
- primary syphilis (1135)
- prion (1159)
- pyelonephritis (1132)
- rehydration therapy (1121)
- rotavirus (1123)
- secondary syphilis (1136)

- secondary tuberculosis (1116)
- septicemia (1142)
- septicemic plague (1148)
- spongiform encephalopathy (1161)
- tertiary syphilis (1136)
- tetanospasmin (1156)
- transcytosis (1155)
- viremia (1142)

Recommended Reading

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Glossary

differential
: In disease, the list of possible causes of an infection.

nosocomial
: Hospital-acquired; commonly refers to an infectious agent.

health care–associated infection (HAI)

Any infection contracted by a patient while receiving treatment for a medical condition at a health care facility, such as hospitals, nursing homes, doctor offices, or rehabilitation centers.

necrotizing fasciitis

Also known as *flesh-eating disease* . A severe skin infection usually caused by the Gram-positive coccus *Streptococcus pyogenes* .

empiric therapy

An approach to treating infection before the infective organism is known, in which multiple antibiotics are administered in an effort to kill the most likely causative agents.

cellulitis

A spreading infection (with inflammation) of connective tissue just below the skin.

granuloma

A thick lesion formed around a site of infection.

secondary tuberculosis

A new round of serious disease that is caused by *Mycobacterium tuberculosis* in patients with latent tuberculosis who have become immunocompromised. Symptoms include severe cough, blood sputum, night sweats, and weight loss.

multisystem inflammatory syndrome in children (MIS-C)

A systemic multi-organ inflammatory syndrome in children brought on by COVID-19 disease.

rehydration therapy

A medical treatment for dehydration, in which a liquid solution of salts and glucose is delivered orally. Also called **oral rehydration therapy (ORT)** .

rotavirus

One of a group of nonenveloped dsRNA viruses that cause severe diarrhea in children.

norovirus

Also known as *Norwalk virus* . A nonenveloped ssRNA virus that causes severe diarrhea in children and adults.

hepatitis

An inflammation of the liver, caused by infection or by exposure to a toxic substance.

hepatitis A virus (HAV)
: A single-stranded RNA picornavirus that causes an acute infection of the liver spread person-to-person by the fecal-oral route.

hepatitis B virus (HBV)
: A partially double-stranded, circular-DNA hepadnavirus that causes diseases of the liver of varying severity, including acute and chronic hepatitis, cirrhosis, and hepatocarcinoma.

hepatitis C virus (HCV)
: A single-stranded, positive-sense, linear-RNA flavivirus that is transmitted by blood transfusions and causes 90% of transfusion-related cases of hepatitis.

cystitis
: Bladder infection.

pyelonephritis
: Kidney infection.

primary syphilis
: The initial inflammatory reaction (chancre) at the site of infection by *Treponema pallidum* .

chancre
: A painless, hard lesion due to an inflammatory reaction at the site of infection by *Treponema pallidum* , the causative agent of syphilis.

secondary syphilis
: A rash that may appear at some point after the primary latent stage of syphilis.

tertiary syphilis
: A final stage of syphilis, manifested by cardiovascular and nervous system symptoms.

congenital syphilis
: Syphilis contracted in utero.

chlamydia
: 1. A pathogenic bacterium lacking a cell wall; chlamydias (or chlamydiae) grow within human or animal cells, transmitting as

elementary bodies to other cells. 2. A disease caused by chlamydia cells. The most frequently reported sexually transmitted disease in the United States. Symptoms range from none, to a burning sensation upon urination, to sterility.

septicemia

An infection of the bloodstream.

viremia

The presence of large numbers of virions in the bloodstream.

bacteremia

A bacterial infection of the blood.

endocarditis

An inflammation of the heart's inner lining.

bubonic plague

A disease caused by the bacterium *Yersinia pestis* ; it is characterized by swollen lymph nodes that often turn black.

septicemic plague

Infection of the bloodstream by *Yersinia pestis* .

pneumonic plague

A highly virulent and contagious *Yersinia pestis* lung infection.

erythema migrans

A bull's-eye rash characteristic of borreliosis (Lyme disease).

Lyme disease

One form of borreliosis. A tick-borne disease caused by *Borrelia burgdorferi* , which may involve skin lesions and arthritis.

borreliosis

Any of a variety of diseases caused by *Borrelia* species and transmitted by ticks or lice. Lyme disease is a form of borreliosis.

blood-brain barrier

A selectively permeable membrane made up of tightly packed capillaries that supply blood to the brain and spinal cord. Large molecules and most pathogens cannot permeate the narrow spaces. Fat-soluble (lipophilic) molecules and oxygen can dissolve through the capillary cell membranes and are absorbed into the brain.

transcytosis

The movement of a cell or substance from one side of a polarized cell to the other side, using an intracellular route.

botulism
: A food-borne disease caused by a *Clostridium botulinum* toxin, involving muscle paralysis.

tetanospasmin
: The tetanus-causing potent exotoxin produced by *Clostridium tetani* .

prion
: An infectious agent that causes propagation of misfolded host proteins; usually consists of a defective version of the host protein.

spongiform encephalopathy
: A brain-wasting disease caused by a prion.