PART II CLINICAL BACTERIOLOGY

CHAPTER 14

Overview of the Major Pathogens & Introduction to Anaerobic Bacteria

CHAPTER CONTENTS

OVERVIEW OF THE MAJOR PATHOGENS

The major bacterial pathogens are presented in Table 14–1 and described in Chapters 15 through 26. So that the reader may concentrate on the important pathogens, the bacteria that are less medically important are described in a separate chapter (see Chapter 27).

Table 14–1 is divided into organisms that are readily Gram stained and those that are not. The readily stained organisms fall into four categories: gram-positive cocci, gram-negative cocci, gram-positive rods, and gram-negative rods. Because there are so many kinds of gram-negative rods, they have been divided into three groups:

(1) Organisms associated with the enteric tract
(2) Organisms associated with the respiratory tract
(3) Organisms from animal sources (zoonotic bacteria)

For ease of understanding, the organisms associated with the enteric tract are further subdivided into three groups: (1) pathogens both inside and outside the enteric tract, (2) pathogens inside the enteric tract, and (3) pathogens outside the enteric tract.

As is true of any classification dealing with biologic entities, this one is not entirely precise. For example, *Campylobacter* causes enteric tract disease but frequently has an animal source. Nevertheless, despite some uncertainties, subdivision of the large number of gram-negative rods into these functional categories should be helpful to the reader.

The organisms that are not readily Gram stained fall into six major categories: *Mycobacterium* species, which are acid-fast rods; *Mycoplasma* species, which have no cell wall and so do not stain with Gram stain; *Treponema* and *Leptospira* species, which are spirochetes too thin to be seen when stained with Gram stain; and *Chlamydia* and *Rickettsia* species, which are very small, intracellular bacteria and are difficult to visualize within the cytoplasm of the cell.

Table 14–2 presents the 10 most common "notifiable" bacterial diseases in the United States for 2012 as compiled by the Centers for Disease Control and Prevention. Note that only notifiable diseases are included and that certain common conditions such as streptococcal pharyngitis and impetigo are not included. Two sexually transmitted diseases, chlamydial infection and gonorrhea, are by far the most common diseases listed, followed by salmonellosis, syphilis, and Lyme disease in the top five.

TABLE 14–1 Major Bacterial Pathogens

Type of Organism	Genus
Readily Gram stained	
Gram-positive cocci	*Staphylococcus, Streptococcus, Enterococcus*
Gram-negative cocci	*Neisseria*
Gram-positive rods	*Corynebacterium, Listeria, Bacillus, Clostridium, Actinomyces, Nocardia*
Gram-negative rods	
Enteric tract organisms	
Pathogenic inside and outside tract	*Escherichia, Salmonella*
Pathogenic primarily inside tract	*Shigella, Vibrio, Campylobacter, Helicobacter*
Pathogenic outside tract	*Klebsiella–Enterobacter–Serratia* group, *Pseudomonas, Proteus–Providencia–Morganella* group, *Bacteroides*
Respiratory tract organisms	*Haemophilus, Legionella, Bordetella*
Organisms from animal sources	*Brucella, Francisella, Pasteurella, Yersinia*
Not readily Gram stained	
Not obligate intracellular bacteria	*Mycobacterium, Mycoplasma, Treponema, Leptospira*
Obligate intracellular bacteria	*Chlamydia, Rickettsia*

INTRODUCTION TO ANAEROBIC BACTERIA

Important Properties

Anaerobes are characterized by their ability to grow only in an atmosphere containing less than 20% oxygen (i.e., they grow poorly if at all in room air). They are a heterogeneous group composed of a variety of bacteria, from those that can barely grow in 20% oxygen to those that can grow only in less than 0.02% oxygen. Table 14–3 describes the optimal oxygen requirements for several representative groups of organisms. The obligate aerobes, such as *Pseudomonas aeruginosa*, grow best in the 20% oxygen of room air and not at all under anaerobic conditions. Facultative anaerobes such as *Escherichia coli* can grow well under either circumstance. Aerotolerant organisms such as *Clostridium histolyticum* can grow to some extent in air but multiply much more rapidly in a lower oxygen concentration. Microaerophilic organisms such as *Campylobacter jejuni* require a reduced oxygen concentration (approximately 5%) to grow optimally. The obligate anaerobes such as *Bacteroides fragilis* and *Clostridium perfringens* require an almost total absence of oxygen. Many anaerobes use nitrogen rather than oxygen as the terminal electron acceptor.

The main reason why the growth of anaerobes is inhibited by oxygen is the reduced amount (or absence) of catalase and superoxide dismutase (SOD) in anaerobes. Catalase and SOD eliminate the toxic compounds hydrogen peroxide and superoxide, which are formed during production of energy by the organism (see Chapter 3). Another reason is the oxidation of essential sulfhydryl groups in enzymes without sufficient reducing power to regenerate them.

In addition to oxygen concentration, the oxidation–reduction potential (E_h) of a tissue is an important determinant of the growth of anaerobes. Areas with low E_h, such as the periodontal pocket, dental plaque, and colon, support the growth of anaerobes well. Crushing injuries that result in devitalized tissue caused by impaired blood supply produce a low E_h, allowing anaerobes to grow and cause disease.

TABLE 14–2 The 10 Most Common Notifiable Bacterial Diseases in the United States in 2012[1]

Disease	Number of Cases
Chlamydial genital infections	1,422,976
Gonorrhea	334,826
Salmonellosis	53,800
Syphilis	49,903
Pertussis	48,277
Lyme disease	30,831
Streptococcus pneumoniae invasive disease	15,635
Shigellosis	15,283
Tuberculosis	9945
Shiga toxin-producing *Escherichia coli*	6463

[1]The latest year for which complete data are available.

Anaerobes of Medical Interest

The anaerobes of medical interest are presented in Table 14–4. It can be seen that they include both rods and cocci and both gram-positive and gram-negative organisms. The rods

TABLE 14–3 Optimal Oxygen Requirements of Representative Bacteria

Bacterial Type	Representative Organism	Growth Under Following Conditions	
		Aerobic	Anaerobic
Obligate aerobes	*Pseudomonas aeruginosa*	3+	0
Facultative anaerobes	*Escherichia coli*	4+	3+
Aerotolerant organisms	*Clostridium histolyticum*	1+	4+
Microaerophiles	*Campylobacter jejuni*	0	1+[1]
Obligate anaerobes	*Bacteroides fragilis*	0	4+

[1] *C. jejuni* grows best (3+) in 5% O_2 plus 10% CO_2. It is also called **capnophilic** in view of its need for CO_2 for optimal growth.

are divided into the spore formers (e.g., *Clostridium*) and the nonspore formers (e.g., *Bacteroides*). In this book, three genera of anaerobes are described as major bacterial pathogens, namely, *Clostridium, Actinomyces,* and *Bacteroides*. *Streptococcus* is a genus of major pathogens consisting of both anaerobic and facultative organisms. The remaining anaerobes are less important and are discussed in Chapter 27.

Clinical Infections

Many of the medically important anaerobes are part of the normal human flora. As such, they are nonpathogens in their normal habitat and cause disease only when they leave those sites. The two prominent exceptions to this are *Clostridium botulinum* and *Clostridium tetani*, the agents of botulism and tetanus, respectively, which are soil organisms. *Clostridium perfringens*, another important human pathogen, is found in the colon and in the soil.

Diseases caused by members of the anaerobic normal flora are characterized by abscesses, which are most frequently located in the brain, lungs, female genital tract, biliary tract, and other intra-abdominal sites. Most abscesses contain more than one organism, either multiple anaerobes or a mixture of anaerobes plus facultative anaerobes. It is thought that the facultative anaerobes consume sufficient oxygen to allow the anaerobes to flourish.

Three important findings on physical examination that arouse suspicion of an anaerobic infection are a foul-smelling discharge, gas in the tissue, and necrotic tissue. In addition, infections in the setting of pulmonary aspiration, bowel surgery, abortion, cancer, or human and animal bites frequently involve anaerobes.

TABLE 14–4 Anaerobic Bacteria of Medical Interest

Morphology	Gram Stain	Genus
Spore-forming rods	+	*Clostridium*
	–	None
Non–spore-forming rods	+	*Actinomyces, Bifidobacterium, Eubacterium, Lactobacillus, Propionibacterium*
	–	*Bacteroides, Fusobacterium*
Non–spore-forming cocci	+	*Peptococcus, Peptostreptococcus, Streptococcus*
	–	*Veillonella*

Laboratory Diagnosis

Two aspects of microbiologic diagnosis of an anaerobic infection are important even before the specimen is cultured: (1) obtaining the appropriate specimen and (2) rapidly transporting the specimen under anaerobic conditions to the laboratory. An appropriate specimen is one that does not contain members of the normal flora to confuse the interpretation. For example, such specimens as blood, pleural fluid, pus, and transtracheal aspirates are appropriate, but sputum and feces are not.

In the laboratory, the cultures are handled and incubated under anaerobic conditions. In addition to the usual diagnostic criteria of Gram stain, morphology, and biochemical reactions, the special technique of gas chromatography is important. In this procedure, organic acids such as formic, acetic, and propionic acids are measured.

Treatment

In general, surgical drainage of the abscess plus administration of antimicrobial drugs are indicated. Drugs commonly used to treat anaerobic infections are penicillin G, cefoxitin, chloramphenicol, clindamycin, and metronidazole. Note, however, that many isolates of the important pathogen *B. fragilis* produce α-lactamase and are thus resistant to penicillin. Note also, that aminoglycosides such as gentamicin are not effective against anaerobes because they require an oxygen-dependent process for uptake into the bacterial cell.

SELF-ASSESSMENT QUESTIONS

1. The main reason why some bacteria are anaerobes (i.e., they cannot grow in the presence of oxygen) is because:

(A) they do not have sufficient catalase and superoxide dismutase.
(B) they have too much ferrous ion that is oxidized to ferric ion in the presence of oxygen.
(C) they have unusual mitochondria that cannot function in the presence of oxygen.
(D) transcription of the gene for the pilus protein is repressed in the presence of oxygen.

2. Which one of the following sets consists of bacteria that are both anaerobes?

(A) *Actinomyces israeli* and *Serratia marcescens*
(B) *Campylobacter jejuni* and *Vibrio cholerae*
(C) *Clostridium perfringens* and *Bacteroides fragilis*
(D) *Mycobacterium tuberculosis* and *Pseudomonas aeruginosa*
(E) *Mycoplasma pneumoniae* and *Corynebacterium diphtheriae*

ANSWERS

1. **(A)**
2. **(C)**

PRACTICE QUESTIONS: USMLE & COURSE EXAMINATIONS

Questions on the topics discussed in this chapter can be found in the Clinical Bacteriology section of Part XIII: USMLE (National Board) Practice Questions starting on page 713. Also see Part XIV: USMLE (National Board) Practice Examination starting on page 751.

CHAPTER

15

Gram-Positive Cocci

CHAPTER CONTENTS

INTRODUCTION

There are two medically important genera of gram-positive cocci: *Staphylococcus* and *Streptococcus.* Two of the most important human pathogens, *Staphylococcus aureus* and *Streptococcus pyogenes,* are described in this chapter. Staphylococci and streptococci are nonmotile and do not form spores.

Both staphylococci and streptococci are gram-positive cocci, but they are distinguished by two main criteria:

(1) Microscopically, staphylococci appear in grapelike clusters, whereas streptococci are in chains.

(2) Biochemically, staphylococci produce catalase (i.e., they degrade hydrogen peroxide), whereas streptococci do not.

Additional information regarding the clinical aspects of infections caused by the organisms in this chapter is provided in Part IX entitled Infectious Diseases beginning on page 593.

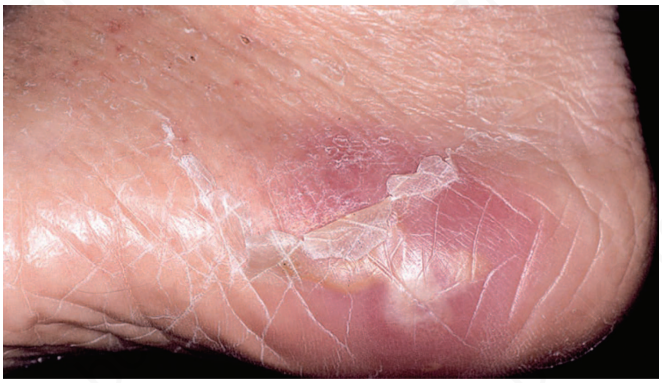

FIGURE 15–1 Abscess on foot. Note central raised area of whitish pus surrounded by erythema. An abscess is the classic lesion caused by *Staphylococcus aureus*. (Reproduced with permission from Wolff K, Johnson R (eds): *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 6th ed. New York: McGraw-Hill, 2009. Copyright © 2009 by The McGraw-Hill Companies, Inc.)

STAPHYLOCOCCUS

Diseases

Staphylococcus aureus causes abscesses (Figure 15–1), various pyogenic infections (e.g., endocarditis, septic arthritis, and osteomyelitis), food poisoning, scalded skin syndrome (Figure 15–2), and toxic shock syndrome. It is one of the most common causes of hospital-acquired pneumonia, septicemia, and surgical-wound infections. It is an important cause of skin and soft tissue infections, such as folliculitis (Figure 15–3), cellulitis, and impetigo (Figure 15–4). It is the most common cause of bacterial conjunctivitis.

Methicillin-resistant Staphylococcus aureus (MRSA) is the most common cause of skin abscesses in the United States. It is also an important cause of pneumonia, necrotizing fasciitis, and sepsis in immunocompetent patients.

Staphylococcus epidermidis causes prosthetic valve endocarditis and prosthetic joint infections. It is the most common cause of central nervous system shunt infections and an important cause of sepsis in newborns. *Staphylococcus saprophyticus* causes urinary tract infections, especially cystitis. Kawasaki syndrome is a disease of unknown etiology that may be caused by certain strains of *S. aureus.*

Important Properties

Staphylococci are spherical gram-positive cocci arranged in irregular grapelike clusters (Figure 15–5). All staphylococci produce **catalase,** whereas no streptococci do (catalase

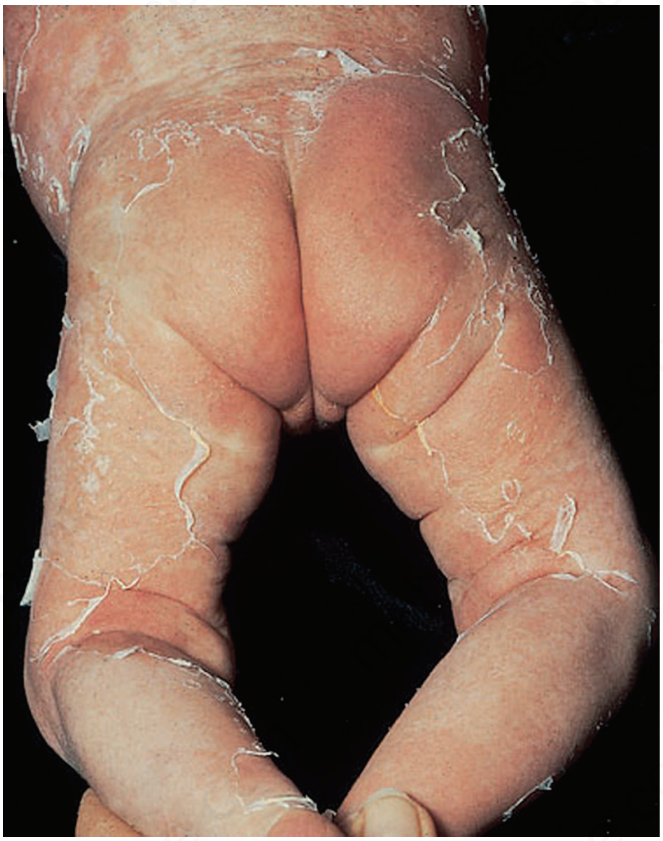

FIGURE 15–2 Scalded skin syndrome. Note widespread areas of "rolled up" desquamated skin in infant. Caused by an exotoxin produced by *Staphylococcus aureus*. (Reproduced with permission from Wolff K, Johnson R (eds): *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 6th ed. New York: McGraw-Hill, 2009. Copyright © 2009 by The McGraw-Hill Companies, Inc.)

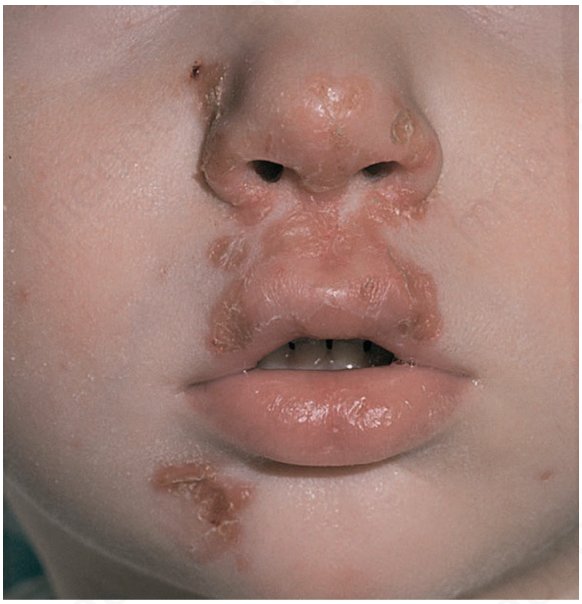

FIGURE 15–4 Impetigo. Lesions of impetigo are crops of vesicles with a "honey-colored" crust. Impetigo is caused by either *Staphylococcus aureus* or *Streptococcus pyogenes*. (Reproduced with permission from Wolff K, Johnson R (eds): *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 6th ed. New York: McGraw-Hill, 2009. Copyright © 2009 by The McGraw-Hill Companies, Inc.)

degrades H_2O_2 into O_2 and H_2O). Catalase is an important virulence factor. Bacteria that make catalase can survive the killing effect of H_2O_2 within neutrophils.

Three species of staphylococci are important human pathogens: *S. aureus*, *S. epidermidis*, and *S. saprophyticus* (Table 15–1). Of these three, *S. aureus* is by far the most

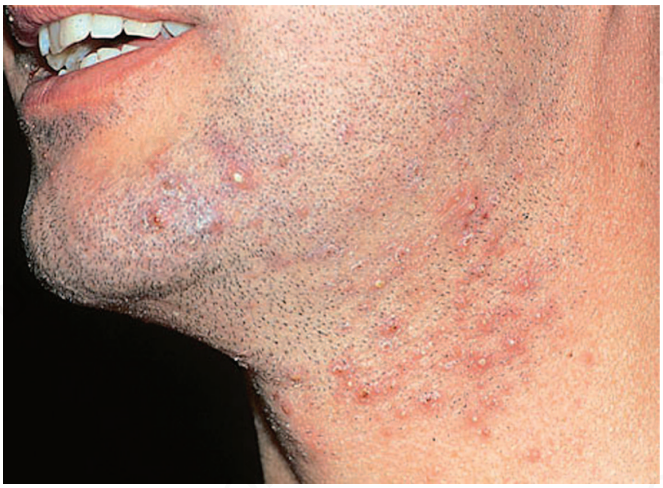

FIGURE 15–3 Folliculitis. Note the multiple, small pustules on the chin and neck. *Staphylococcus aureus* is the most common cause of folliculitis. (Reproduced with permission from Wolff K, Goldsmith LA, Katz SI et al (eds): *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York: McGraw-Hill, 2008, pg 1699. Copyright © 2008 by The McGraw-Hill Companies, Inc.)

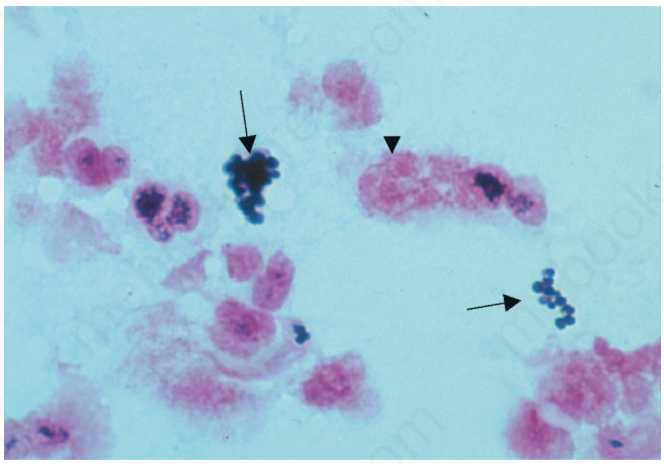

FIGURE 15–5 *Staphylococcus aureus*—Gram stain. Arrows point to two "grapelike" clusters of gram-positive cocci. Arrowhead points to neutrophil with pink segmented nuclei. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

TABLE 15–1 Staphylococci of Medical Importance

Species	Coagulase Production	Typical Hemolysis	Important Features[1]	Typical Disease
S. aureus	+	β	Protein A on surface	Abscess, food poisoning, toxic shock syndrome
S. epidermidis	–	None	Sensitive to novobiocin	Infection of prosthetic heart valves and hips; common member of skin flora
S. saprophyticus	–	None	Resistant to novobiocin	Urinary tract

[1]All staphylococci are catalase-positive.

common and causes the most serious infections. *Staphylococcus aureus* is distinguished from the others primarily by **coagulase** production (Figure 15–6). **Coagulase** is an enzyme that causes plasma to clot by activating prothrombin to form thrombin. Thrombin then catalyzes the activation of fibrinogen to form the fibrin clot. *Staphylococcus epidermidis* and *S. saprophyticus* are often referred to as coagulase-negative staphylococci.

Staphylococcus aureus produces a carotenoid pigment called **staphyloxanthin,** which imparts a golden color to its colonies. This pigment enhances the pathogenicity of the organism by inactivating the microbicidal effect of superoxides and other reactive oxygen species within neutrophils. *Staphylococcus epidermidis* does not synthesize this pigment and produces white colonies. The virulence of *S. epidermidis* is significantly less than that of *S. aureus.*

Two other characteristics further distinguish these species, namely, *S. aureus usually ferments mannitol and hemolyzes red blood cells,* whereas *S. epidermidis* and *S. saprophyticus* do not. Hemolysis of red cells by hemolysins produced by *S. aureus* is the source of iron required for growth of the organism. The iron in hemoglobin is recovered by the bacteria and utilized in the synthesis of cytochrome enzymes used to produce energy.

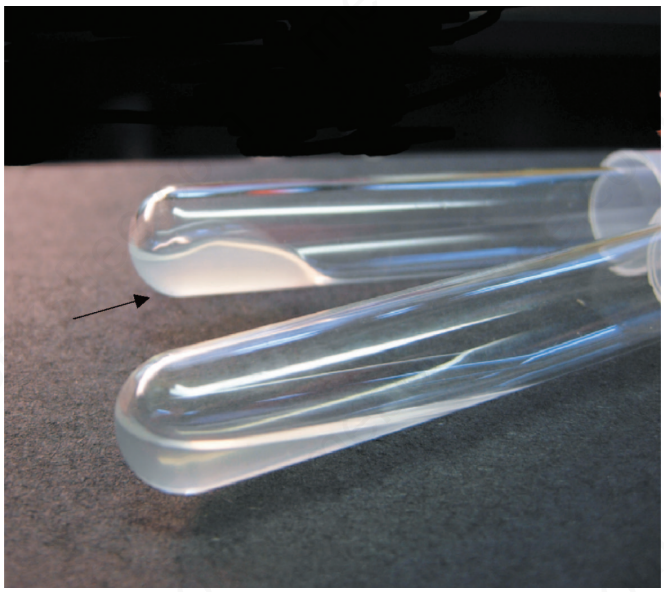

FIGURE 15–6 Coagulase test—Upper tube inoculated with *Staphylococcus aureus;* lower tube inoculated with *Staphylococcus epidermidis*. Arrow points to clotted plasma formed by coagulase produced by *S. aureus*. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

More than 90% of *S. aureus* strains contain plasmids that encode **β-lactamase**, the enzyme that degrades many, but not all, penicillins. Some strains of *S. aureus* are resistant to the β-lactamase–resistant penicillins, such as methicillin and nafcillin, by virtue of changes in the **penicillin-binding proteins** (PBP) in their cell membrane. Genes on the bacterial chromosome called *mecA* genes encode these altered PBPs.

These strains are commonly known as *methicillin-resistant S. aureus* (MRSA) or nafcillin-resistant *S. aureus* (NRSA). MRSA causes both health care-acquired (HCA-MRSA) and community-acquired (CA-MRSA) infections. MRSA currently accounts for more than 50% of *S. aureus* strains isolated from hospital patients in the United States. CA-MRSA is a very common cause of community-acquired staphylococcal infections. Almost all strains of CA-MRSA produce P-V leukocidin (see later) whereas relatively few strains of HCA-MRSA do so. The most common strain of MRSA in the United States is the "USA300" strain.

Strains of *S. aureus* with intermediate resistance to vancomycin (VISA) and with full resistance to vancomycin (VRSA) have also been detected. The cassette of genes that encodes vancomycin resistance in *S. aureus* is the same as the cassette that provides vancomycin resistance in enterococci. These genes are located in a transposon on a plasmid and encode the enzymes that **substitute D-lactate for D-alanine** in the peptidoglycan.

S. aureus has several important cell wall components and antigens:

(1) **Protein A** is the major protein in the cell wall. It is an important virulence factor because it binds to the Fc portion of IgG at the complement-binding site, thereby preventing the activation of complement. As a consequence, no C3b is produced, and the opsonization and phagocytosis of the organisms are greatly reduced. Protein A is used in certain tests in the clinical laboratory because it binds to IgG and forms a "coagglutinate" with antigen–antibody complexes. The coagulase-negative staphylococci do not produce protein A.

(2) **Teichoic acids** are polymers of ribitol phosphate. They mediate adherence of the staphylococci to mucosal cells. **Lipoteichoic acids** play a role in the induction of septic shock by inducing cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) from macrophages (See the discussion of septic shock in the Endotoxin section of Chapter 7).

(3) Polysaccharide capsule is also an important virulence factor. There are 11 serotypes based on the antigenicity of the capsular polysaccharide, but types 5 and 8 cause 85% of infections. Some strains of *S. aureus* are coated with a small amount of polysaccharide capsule, called a microcapsule. The capsule is poorly immunogenic, which has made producing an effective vaccine difficult.

(4) Surface receptors for specific staphylococcal bacteriophages permit the "phage typing" of strains for epidemiologic purposes. Teichoic acids make up part of these receptors.

(5) The peptidoglycan of *S. aureus* has endotoxin-like properties (i.e., it can stimulate macrophages to produce cytokines and can activate the complement and coagulation cascades). This explains the ability of *S. aureus* to cause the clinical findings of septic shock yet not possess endotoxin.

Transmission

Humans are the reservoir for staphylococci. The **nose is the main site of colonization of** *S. aureus,* and approximately 30% of people are colonized at any one time. People who are chronic carriers of *S. aureus* in their nose have an increased risk of skin infections caused by *S. aureus*.

The skin, especially of hospital personnel and patients, is also a common site of *S. aureus* colonization. Hand contact is an important mode of transmission, and handwashing decreases transmission.

Staphylococcus aureus is also found in the vagina of approximately 5% of women, which predisposes them to toxic shock syndrome. Additional sources of staphylococcal infection are shedding from human lesions and fomites such as towels and clothing contaminated by these lesions.

Disease caused by *S. aureus* is favored by a heavily contaminated environment (e.g., family members with boils) and a compromised immune system. Reduced humoral immunity, including low levels of antibody, complement, or neutrophils, especially predisposes to staphylococcal infections. Diabetes and intravenous drug use predispose to infections by *S. aureus.* Patients with chronic granulomatous disease (CGD), a disease characterized by a defect in the ability of neutrophils to kill bacteria, are especially prone to *S. aureus* infections (see Chapter 68).

Staphylococcus epidermidis is found primarily on the human skin and can enter the bloodstream at the site of intravenous catheters that penetrate through the skin. *Staphylococcus saprophyticus* is found primarily on the mucosa of the genital tract in young women and from that site can ascend into the urinary bladder to cause urinary tract infections.

Pathogenesis

Staphylococcus aureus

Staphylococcus aureus causes disease both by producing toxins and by inducing pyogenic inflammation. The typical lesion of *S. aureus* infection is an **abscess.** Abscesses undergo central necrosis and usually drain to the outside (e.g., furuncles and boils), but organisms may disseminate via the bloodstream as well. **Foreign bodies,** such as sutures and intravenous catheters, are important predisposing factors to infection by *S. aureus.*

Several important toxins and enzymes are produced by *S. aureus.* The three clinically important exotoxins are enterotoxin, toxic shock syndrome toxin, and exfoliatin.

(1) **Enterotoxin** causes food poisoning characterized by prominent vomiting and watery, nonbloody diarrhea. It acts as a **superantigen** within the gastrointestinal tract to stimulate the release of large amounts of IL-1 and IL-2 from macrophages and helper T cells, respectively. The prominent vomiting appears to be caused by cytokines released from the lymphoid cells, which stimulate the enteric nervous system to activate the vomiting center in the brain. Enterotoxin is fairly heat-resistant and is therefore usually not inactivated by brief cooking. It is resistant to stomach acid and to enzymes in the stomach and jejunum. There are six immunologic types of enterotoxin, types A–F.

(2) **Toxic shock syndrome toxin** (TSST) causes toxic shock, especially in tampon-using menstruating women or in individuals with wound infections. Toxic shock also occurs in patients with nasal packing used to stop bleeding from the nose. TSST is produced locally by *S. aureus* in the vagina, nose, or other infected site. The toxin enters the bloodstream, causing a toxemia. Blood cultures typically do not grow *S. aureus.*

TSST is a **superantigen** and causes toxic shock by stimulating the release of large amounts of IL-1, IL-2, and TNF (see the discussions of exotoxins in Chapter 7 and superantigens in Chapter 58). Approximately 5% to 25% of isolates of *S. aureus* carry the gene for TSST. Toxic shock occurs in people who do not have antibody against TSST.

(3) **Exfoliatin** causes "scalded skin" syndrome in young children. It is "epidermolytic" and acts as a **protease that cleaves desmoglein** in desmosomes, leading to the separation of the epidermis at the granular cell layer.

(4) Several exotoxins can kill leukocytes (leukocidins) and cause necrosis of tissues in vivo. Of these, the two most important are alpha toxin and P-V leukocidin. **Alpha toxin** causes marked necrosis of the skin and hemolysis. The cytotoxic effect of alpha toxin is attributed to the formation of holes in the cell membrane and the consequent loss of low-molecular-weight substances from the damaged cell.

P-V leukocidin is a **pore-forming toxin** that kills cells, especially white blood cells, by damaging cell membranes. The two subunits of the toxin assemble in the cell membrane to form a pore through which cell contents leak out. The gene encoding P-V leukocidin is located on a lysogenic phage. P-V leukocidin is an important virulence factor for CA-MRSA and plays a role in the severe skin and soft tissue infection caused by this organism. A severe necrotizing pneumonia is also caused by strains of *S. aureus* that produce P-V leukocidin. Approximately 2% of clinical isolates of *S. aureus* produce P-V leukocidin.

(5) The enzymes include **coagulase,** fibrinolysin, hyaluronidase, proteases, nucleases, and lipases. Coagulase, by clotting plasma, serves to wall off the infected site, thereby retarding the migration of neutrophils into the site. Staphylokinase is a fibrinolysin that can lyse thrombi.

Staphylococcus epidermidis & Staphylococcus saprophyticus

Unlike *S. aureus,* these two coagulase-negative staphylococci do not produce exotoxins. Thus, they do not cause food poisoning or toxic shock syndrome. They do, however, cause pyogenic infections. For example, *S. epidermidis* is a prominent cause of pyogenic infections on prosthetic implants such as heart valves and hip joints, and *S. saprophyticus* causes urinary tract infections, especially cystitis.

Clinical Findings

The important clinical manifestations caused by *S. aureus* can be divided into two groups: pyogenic (pus-producing) and toxin-mediated (Table 15–2). *Staphylococcus aureus* is a major cause of skin, soft tissue, bone, joint, lung, heart, and kidney infections. Pyogenic diseases are the first group described, and toxin-mediated diseases are the second group.

Staphylococcus aureus: Pyogenic Diseases

(1) Skin and soft tissue infections are very common. These include abscess (see Figure 15–1), impetigo (see Figure 15–4), furuncles, carbuncles (Figure 15–7), paronychia, cellulitis, folliculitis (see Figure 15–3), hidradenitis suppurativa, conjunctivitis, eyelid infections (blepharitis and hordeolum), and postpartum breast infections (mastitis). Lymphangitis can occur, especially on the forearm associated with an infection on the hand.

Severe necrotizing skin and soft tissue infections are caused by MRSA strains that produce P-V leukocidin. These infections are typically community-acquired rather than hospital-acquired. In the United States, community-acquired MRSA (CA-MRSA) strains are the most common cause of skin and soft tissue infections. These CA-MRSA strains are an especially common cause of infection among the homeless and intravenous drug users. Athletes who engage in close personal contact such as wrestlers and football players are also at risk. Note that hospital-acquired MRSA (HA-MRSA) causes approximately 50% of all nosocomial *S. aureus* infections. Molecular analysis reveals that the CA-MRSA strains are different from the HA-MRSA strains.

(2) Septicemia (sepsis) can originate from any localized lesion, especially wound infection, or as a result of intravenous drug abuse. Sepsis caused by *S. aureus* has clinical features similar to those of sepsis caused by certain gram-negative bacteria, such as *Neisseria meningitidis* (see Chapter 16).

(3) Endocarditis may occur on normal or prosthetic heart valves, especially right-sided endocarditis (tricuspid valve) in intravenous drug users. (Prosthetic valve endocarditis is often caused by *S. epidermidis*.)

(4) Osteomyelitis and septic arthritis may arise either by hematogenous spread from a distant infected focus or be introduced locally at a wound site. *Staphylococcus aureus* is a very common cause of these diseases, especially in children.

TABLE 15–2 Important Features of Pathogenesis by Staphylococci

Organism	Type of Pathogenesis	Typical Disease	Predisposing Factor	Mode of Prevention
S. aureus	1. Toxigenic (superantigen)	Toxic shock syndrome	Vaginal or nasal tampons	Reduce time of tampon use
		Food poisoning	Improper food storage	Refrigerate food
	2. Pyogenic (abscess)			
	a. Local	Skin infection (e.g., impetigo, surgical-wound infections)	Poor skin hygiene; failure to follow aseptic procedures	Cleanliness; handwashing; reduce nasal carriage
	b. Disseminated	Sepsis, endocarditis[1]	IV drug use	Reduce IV drug use
S. epidermidis	Pyogenic	Infections of intravenous catheter sites and prosthetic devices	Failure to follow aseptic procedures or remove IV catheters promptly	Handwashing; remove IV catheters promptly
S. saprophyticus	Pyogenic	Urinary tract infection	Sexual activity	

IV = intravenous.

[1]For simplicity, many forms of disseminated diseases caused by *S. aureus* (e.g., osteomyelitis, arthritis) were not included in the table.

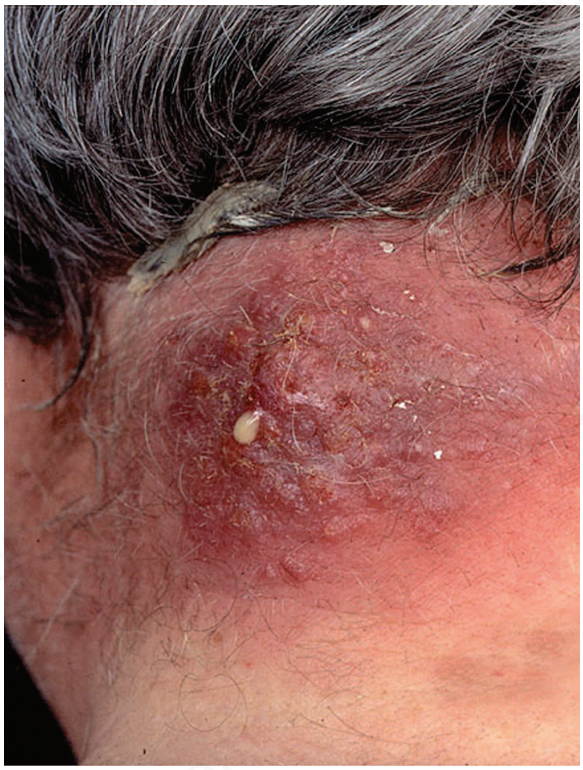

FIGURE 15–7 Carbuncle. A carbuncle is a multiheaded abscess often located on the back of the neck. Note drop of yellowish pus near the center of the lesion. Carbuncles are caused by *Staphylococcus aureus*. (Reproduced with permission from Wolff K, Johnson R (eds): *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 6th ed. New York: McGraw-Hill, 2009. Copyright © 2009 by The McGraw-Hill Companies, Inc.)

(5) *Staphylococcus aureus* is the most common cause of postsurgical wound infections which are an important cause of morbidity and mortality in hospitals. For example, *S. aureus* and *S. epidermidis* are the most common causes of infections at the site where cardiac pacemakers are installed.

(6) Pneumonia can occur in postoperative patients or following viral respiratory infection, especially influenza. Staphylococcal pneumonia often leads to empyema or lung abscess. In many hospitals, it is the most common cause of nosocomial pneumonia in general and especially of ventilator-associated pneumonia in intensive care units. CA-MRSA causes a severe necrotizing pneumonia.

(7) Conjunctivitis typically presents with unilateral burning eye pain, hyperemia of the conjunctiva, and a purulent discharge. The organism is transmitted to the eye by contaminated fingers. *Staphylococcus aureus* is the most common cause overall, but *S. pneumoniae* and *Haemophilus influenzae* are more common in children. Gonococcal and nongonococcal (caused by *Chlamydia trachomatis*) conjunctivitis is acquired by infants during passage through the birth canal.

(8) Abscesses can occur in any organ when *S. aureus* circulates in the bloodstream (bacteremia). These abscesses are often called "metastatic abscesses" because they occur by the spread of bacteria from the original site of infection, often in the skin.

Staphylococcus aureus: Toxin-Mediated Diseases

(1) Food poisoning (gastroenteritis) is caused by ingestion of enterotoxin, which is preformed in foods and hence has a short incubation period (1–8 hours). In staphylococcal food poisoning, vomiting is typically more prominent than diarrhea.

(2) Toxic shock syndrome is characterized by fever; hypotension; a diffuse, macular, sunburn-like rash that goes on to desquamate; and involvement of three or more of the following organs: liver, kidney, gastrointestinal tract, central nervous system, muscle, or blood.

(3) Scalded-skin syndrome is characterized by fever, large bullae, and an erythematous macular rash. Large areas of skin slough, serous fluid exudes, and electrolyte imbalance can occur. Hair and nails can be lost. Recovery usually occurs within 7–10 days. This syndrome occurs most often in young children.

Staphylococcus aureus: Kawasaki Disease

Kawasaki disease (KD) is a disease of unknown etiology that is discussed here because several of its features resemble toxic shock syndrome caused by the superantigens of *S. aureus* (and *S. pyogenes*). KD is a vasculitis involving small and medium-size arteries, especially the coronary arteries. It is the most common cause of acquired heart disease in children in the United States.

Clinically, KD is characterized by a high fever of at least 5 days' duration; bilateral nonpurulent conjunctivitis; lesions of the lips and oral mucosa (e.g., strawberry tongue, edema of the lips, and erythema of the oropharynx); cervical lymphadenopathy; a diffuse erythematous, maculopapular rash; and erythema and edema of the hands and feet that often ends with desquamation.

The most characteristic clinical finding of KD is cardiac involvement, especially myocarditis, arrhythmias, and regurgitation involving the mitral or aortic valves. The main cause of morbidity and mortality in KD is **aneurysm of the coronary arteries**.

KD is much more common in children of Asian ancestry, leading to speculation that certain major histocompatibility complex (MHC) alleles may predispose to the disease. It is a disease of children younger than 5 years of age, often occurring in mini-outbreaks. It occurs worldwide but is much more common in Japan.

There is no definitive diagnostic laboratory test for KD. Effective therapy consists of high-dose immune globulins (IVIG) plus high-dose aspirin, which promptly reduce the fever and other symptoms and, most importantly, significantly reduce the occurrence of aneurysms.

Staphylococcus epidermidis & Staphylococcus saprophyticus

Two **coagulase-negative** staphylococci are common human pathogens: *S. epidermidis* and *S. saprophyticus. Staphylococcus epidermidis* infections are almost always hospital-acquired, whereas *S. saprophyticus* infections are almost always community-acquired.

Staphylococcus epidermidis is part of the normal human flora on the skin and mucous membranes but can enter the bloodstream (bacteremia) and cause metastatic infections, especially at the site of implants. It commonly infects intravenous catheters and prosthetic implants (e.g., prosthetic heart valves [endocarditis], vascular grafts, and prosthetic joints [arthritis or osteomyelitis]) (see Table 15–2). *Staphylococcus epidermidis* is also a major cause of sepsis in neonates and of peritonitis in patients with renal failure who are undergoing peritoneal dialysis through an indwelling catheter. It is the most common bacterium to cause cerebrospinal fluid shunt infections.

Strains of *S. epidermidis* that produce a glycocalyx are more likely to adhere to prosthetic implant materials and therefore are more likely to infect these implants than strains that do not produce a glycocalyx. Hospital personnel are a major reservoir for antibiotic-resistant strains of *S. epidermidis.*

Staphylococcus saprophyticus causes urinary tract infections, particularly in sexually active young women. Most women with this infection have had sexual intercourse within the previous 24 hours. This organism is second to *Escherichia coli* as a cause of community-acquired urinary tract infections in young women.

Staphylococcus lugdenensis is a relatively uncommon coagulase-negative staphylococcus that causes prosthetic valve endocarditis and skin infections.

Laboratory Diagnosis

Smears from staphylococcal lesions reveal gram-positive cocci in grapelike clusters (see Figure 15–5). Cultures of *S. aureus* typically yield golden-yellow colonies that are usually β-hemolytic. *Staphylococcus aureus* is **coagulase-positive** (see Figure 15–6). Mannitol-salt agar is a commonly used screening device for *S. aureus. Staphylococcus aureus* ferments mannitol, which lowers the pH causing the agar to turn yellow whereas *S. epidermidis* does not ferment mannitol and the agar remains pink.

Cultures of coagulase-negative staphylococci typically yield white colonies that are nonhemolytic. The two coagulase-negative staphylococci are distinguished by their reaction to the antibiotic novobiocin: *S. epidermidis* is sensitive, whereas *S. saprophyticus* is resistant. There are no serologic or skin tests used for the diagnosis of any acute staphylococcal infection.

In toxic shock syndrome, isolation of *S. aureus* is not required to make a diagnosis as long as the clinical criteria are met. Laboratory findings that support a diagnosis of toxic shock syndrome include the isolation of a TSST-producing strain of *S. aureus* and development of antibodies to the toxin during convalescence, although the latter is not useful for diagnosis during the acute disease.

For epidemiologic purposes, *S. aureus* can be subdivided into subgroups based on the susceptibility of the clinical isolate to lysis by a variety of bacteriophages. A person carrying *S. aureus* of the same phage group as that which caused the outbreak may be the source of the infections.

Treatment

In the United States, 90% or more of *S. aureus* strains are resistant to penicillin G. Most of these strains produce **β-lactamase.** Such organisms can be treated with β-lactamase–resistant penicillins (e.g., nafcillin or cloxacillin), some cephalosporins, or vancomycin. Treatment with a combination of a β-lactamase–sensitive penicillin (e.g., amoxicillin) and a β-lactamase inhibitor (e.g., clavulanic acid) is also useful.

Approximately 20% of *S. aureus* strains are **methicillin-resistant** or nafcillin-resistant by virtue of altered penicillin-binding proteins. These resistant strains of *S. aureus* are often abbreviated **MRSA** or NRSA, respectively. Such organisms can produce sizable outbreaks of disease, especially in hospitals. The drug of choice for these staphylococci is vancomycin, to which gentamicin is sometimes added. Daptomycin is also useful. Trimethoprim-sulfamethoxazole or clindamycin can be used to treat non–life-threatening infections caused by these organisms. Note that MRSA strains are resistant to almost all β-lactam drugs, including both penicillins and cephalosporins. Ceftaroline fosamil is the first β-lactam drug useful for the treatment of MRSA infections.

Strains of *S. aureus* with intermediate resistance to vancomycin (VISA strains) and with complete resistance to vancomycin (VRSA strains) have been isolated from patients. These strains are typically methicillin-/nafcillin-resistant as well, which makes them very difficult to treat. Daptomycin (Cubicin) can be used to treat infections by these organisms. Quinupristin-dalfopristin (Synercid) is another useful choice.

The treatment of toxic shock syndrome involves correction of the shock by using fluids, pressor drugs, and inotropic drugs; administration of a β-lactamase–resistant penicillin such as nafcillin; and removal of the tampon or debridement of the infected site as needed. Pooled serum globulins, which contain antibodies against TSST, may be useful.

Mupirocin is very effective as a topical antibiotic in skin infections caused by *S. aureus.* It has also been used to reduce nasal carriage of the organism in hospital personnel and in patients with recurrent staphylococcal infections. A topical skin antiseptic, such as chlorhexidine, can be added to mupirocin.

Some strains of staphylococci exhibit **tolerance** (i.e., they can be inhibited by antibiotics but are not killed). (That is, the ratio of minimum bactericidal concentration [MBC] to minimum inhibitory concentration [MIC] is very high.) Tolerance may result from failure of the drugs to inactivate inhibitors of autolytic enzymes that degrade the organism. Tolerant organisms should be treated with drug combinations (see Chapter 10).

Drainage (spontaneous or surgical) is the cornerstone of abscess treatment. **Incision and drainage (I&D)** is often sufficient treatment for a skin abscess (e.g., furuncle [boil]); antibiotics are not necessary in most cases. Previous infection provides only partial immunity to reinfection.

Staphylococcus epidermidis is highly antibiotic resistant. Most strains produce β-lactamase but are sensitive to β-lactamase–resistant drugs such as nafcillin. These are called methicillin-sensitive strains (MSSE). Some strains are methicillin/nafcillin resistant (MRSE) due to altered penicillin-binding proteins. The drug of choice is vancomycin, to which either rifampin or an aminoglycoside can be added. Removal of the catheter or other device is often necessary. *Staphylococcus saprophyticus* urinary tract infections can be treated with trimethoprim-sulfamethoxazole or a quinolone, such as ciprofloxacin.

Prevention

There is no vaccine against staphylococci. Cleanliness, frequent handwashing, and aseptic management of lesions help to control spread of *S. aureus.* Persistent colonization of the nose by *S. aureus* can be reduced by intranasal mupirocin or by oral antibiotics, such as ciprofloxacin or trimethoprim-sulfamethoxazole, but is difficult to eliminate completely. Shedders may have to be removed from high-risk areas (e.g., operating rooms and newborn nurseries). Cefazolin is often used perioperatively to prevent staphylococcal surgical-wound infections.

STREPTOCOCCUS

Streptococci of medical importance are listed in Table 15–3. All but one of these streptococci are discussed in this section; *S. pneumoniae* is discussed separately at the end of this chapter because it is so important.

Diseases

Streptococci cause a wide variety of infections. *Streptococcus pyogenes* (group A streptococcus) is the leading bacterial cause of pharyngitis (Figure 15–8) and cellulitis (Figure 15–9). It is an important cause of impetigo (see Figure 15–3), necrotizing fasciitis, and streptococcal toxic shock syndrome. It is also the inciting factor of two important immunologic diseases, namely, rheumatic fever and acute glomerulonephritis. *Streptococcus agalactiae* (group B streptococcus) is the leading cause of neonatal sepsis and meningitis. *Enterococcus faecalis* is an important cause of hospital-acquired urinary tract infections and endocarditis. Viridans group streptococci are the most common cause of endocarditis (Figure 15–10). *Streptococcus bovis* (also known as *Streptococcus gallolyticus*) is an uncommon cause of endocarditis.

Important Properties

Streptococci are spherical gram-positive cocci arranged in chains or pairs (Figure 15–11). All streptococci are **catalase-negative,** whereas staphylococci are catalase-positive (see Table 15–3).

One of the most important characteristics for identification of streptococci is the type of hemolysis (Figure 15–12).

(1) **α-Hemolytic** streptococci form a green zone around their colonies as a result of incomplete lysis of red blood cells in the agar. The green color is formed when hydrogen peroxide produced by the bacteria oxidizes hemoglobin (red color) to biliverdin (green color).

TABLE 15–3 Streptococci of Medical Importance

Species	Lancefield Group	Typical Hemolysis	Diagnostic Features[1]
S. pyogenes	A	β	Bacitracin-sensitive
S. agalactiae	B	β	Bacitracin-resistant; hippurate hydrolyzed
E. faecalis	D	α or β or none	Growth in 6.5% NaCl[2]
S. bovis[3]	D	α or none	No growth in 6.5% NaCl
S. pneumoniae	NA[4]	α	Bile-soluble; inhibited by optochin
Viridans group[5]	NA	α	Not bile-soluble; not inhibited by optochin

[1]All streptococci are catalase-negative.

[2]Both *E. faecalis* and *S. bovis* grow on bile-esculin agar, whereas other streptococci do not. They hydrolyze the esculin, and this results in a characteristic black discoloration of the agar.

[3]*Streptococcus bovis* is a nonenterococcal group D organism.

[4]NA, not applicable.

[5]Viridans group streptococci include several species, such as *S. sanguinis, S. mutans, S. mitis, S. gordonii, S. salivarius, S. anginosus, S. milleri,* and *S. intermedius*.

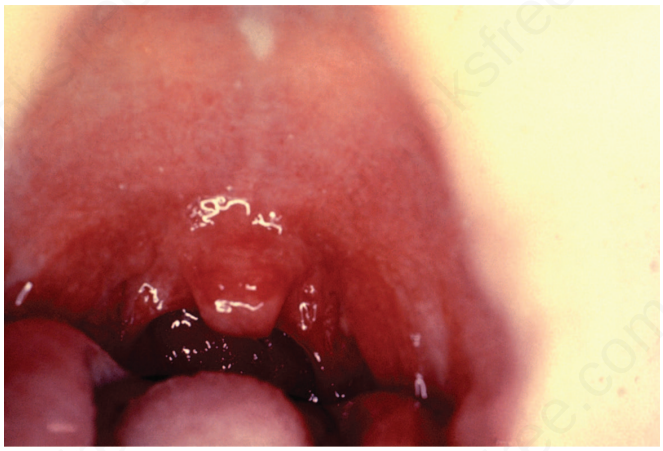

FIGURE 15–8 Pharyngitis. Note erythema of soft palate, uvula, and posterior pharynx and swelling of the uvula. The most common bacterial cause of pharyngitis is *Streptococcus pyogenes*. Note: The curved white lines on the uvula and the palate are artifacts of photography. (Source: Centers for Disease Control and Prevention. CDC #6323.)

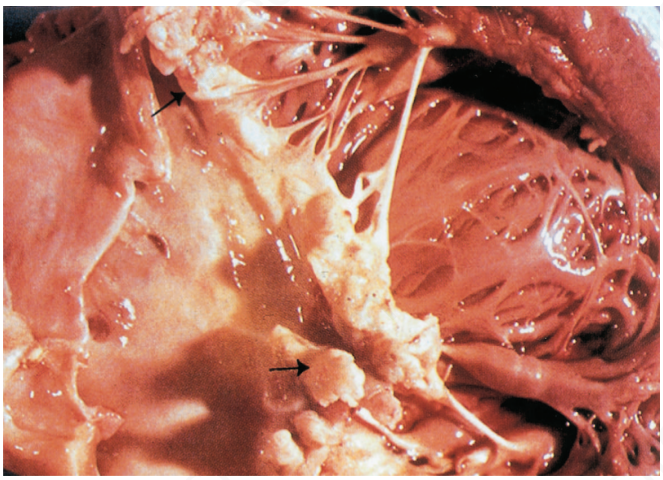

FIGURE 15–10 Endocarditis. Note vegetations (black arrows) on mitral valve. Viridans streptococci are the most common cause of subacute bacterial endocarditis. (Reproduced with permission from Longo DL et al (eds): *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill, 2012, pg 1052. Copyright © 2012 by The McGraw-Hill Companies, Inc.)

(2) **β-Hemolytic** streptococci form a clear zone around their colonies because complete lysis of the red cells occurs. β-Hemolysis is due to the production of enzymes (hemolysins) called streptolysin O and streptolysin S (see "Pathogenesis" later).

(3) Some streptococci are nonhemolytic (γ-hemolysis).

There are two important antigens of β-hemolytic streptococci:

(1) **C carbohydrate** determines the *group* of β-hemolytic streptococci. It is located in the cell wall, and its specificity is determined by an amino sugar. For example, Group A β-hemolytic streptococci (*S. pyogenes*) is distinguished from Group B β-hemolytic streptococci (*S. agalactiae*) because it has a different C carbohydrate.

(2) **M protein** is the most important virulence factor of *S. pyogenes*. It protrudes from the outer surface of the cell and blocks phagocytosis (i.e., it is **antiphagocytic**). It inactivates C3b, a component of complement that opsonizes the bacteria prior to phagocytosis (see Chapter 63). Strains of *S. pyogenes* that do *not* produce M protein are nonpathogenic.

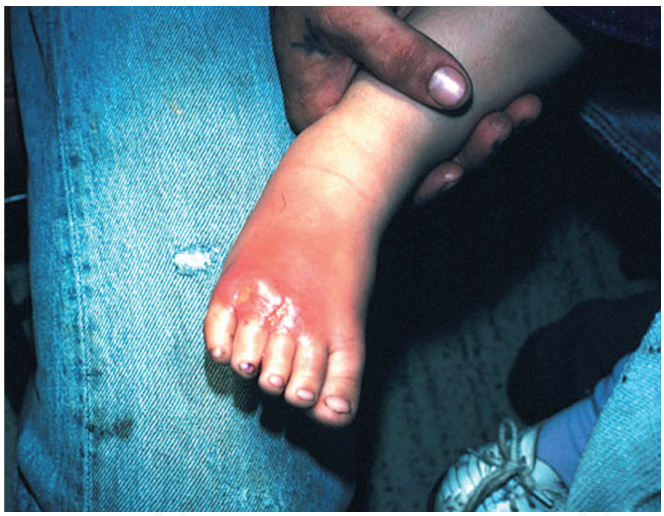

FIGURE 15–9 Cellulitis. Note erythema and swelling of the dorsum of the foot. *Streptococcus pyogenes* is the most common cause of cellulitis. (Reproduced with permission from Usatine, RP et al: *The Color Atlas of Family Medicine*, New York: McGraw-Hill, 2009. Courtesy of Richard P. Usatine, MD.)

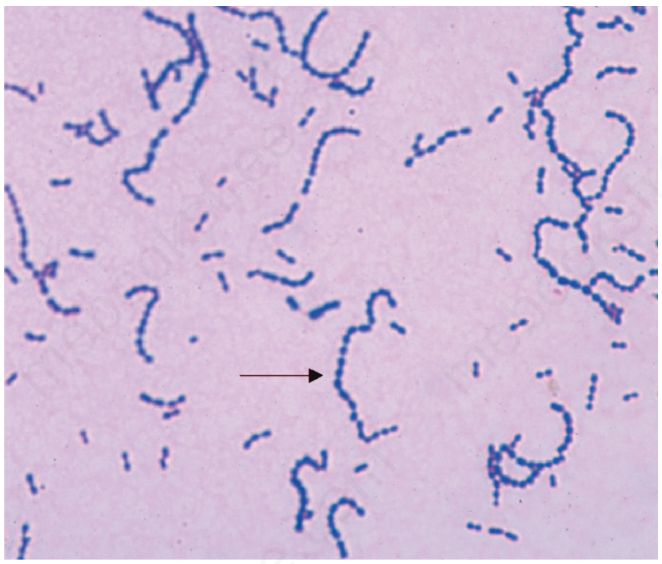

FIGURE 15–11 *Streptococcus pyogenes*—Gram stain. Arrow points to a long chain of gram-positive cocci. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

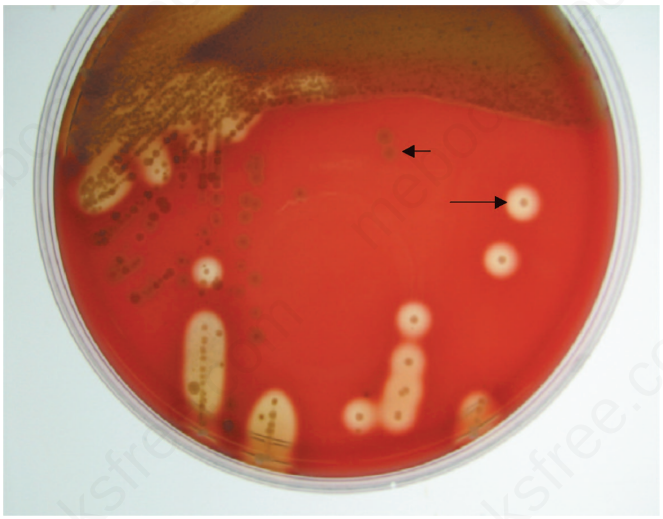

FIGURE 15–12 α-Hemolysis and β-hemolysis on blood agar—Short arrow points to an α-hemolytic colony, probably a viridans group streptococcus. Long arrow points to a β-hemolytic colony, probably *Streptococcus pyogenes*. The specimen was a throat swab taken from a person with a sore throat. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

M protein also determines the *type* of group A β-hemolytic streptococci. There are approximately 100 serotypes based on the M protein, which explains why multiple infections with *S. pyogenes* can occur. Antibody to M protein provides type-specific immunity.

Strains of *S. pyogenes* that produce certain M protein types are **rheumatogenic** (i.e., cause primarily rheumatic fever), whereas strains of *S. pyogenes* that produce other M protein types are **nephritogenic** (i.e., cause primarily acute glomerulonephritis). Although M protein is the main antiphagocytic component of *S. pyogenes,* the organism also has a polysaccharide capsule that plays a role in retarding phagocytosis.

Classification of Streptococci

β-Hemolytic Streptococci

These are arranged into groups A–U (known as Lancefield groups) on the basis of antigenic differences in C carbohydrate. In the clinical laboratory, the group is determined by precipitin tests with specific antisera or by immunofluorescence.

Group A streptococci (*S. pyogenes*) are one of the most important human pathogens. They are the most frequent bacterial cause of pharyngitis and a very common cause of skin infections. They adhere to pharyngeal epithelium via pili composed of lipoteichoic acid and M protein. Many strains have a hyaluronic acid capsule that is antiphagocytic. The growth of *S. pyogenes* on agar plates in the laboratory is inhibited by the antibiotic bacitracin, an important diagnostic criterion (Figure 15–13).

Group B streptococci (*S. agalactiae*) colonize the genital tract of some women and can cause neonatal meningitis and sepsis. They are usually bacitracin-resistant. They hydrolyze (break down) hippurate, an important diagnostic criterion.

Group D streptococci include enterococci (e.g., *E. faecalis* and *Enterococcus faecium*) and nonenterococci (e.g., *S. bovis*). Enterococci are members of the normal flora of the colon and are noted for their ability to cause urinary, biliary, and cardiovascular infections. They are very hardy organisms; they can grow in hypertonic (6.5%) saline or in bile and are not killed by penicillin G. As a result, a synergistic combination of penicillin and an aminoglycoside (e.g., gentamicin) is required to kill enterococci. Vancomycin can also be used, but vancomycin-resistant enterococci (VRE) have emerged and become an important and much feared cause of life-threatening nosocomial infections. More strains of *E. faecium* are vancomycin-resistant than are strains of *E. faecalis.*

Nonenterococcal group D streptococci, such as *S. bovis,* can cause similar infections but are much less hardy organisms (e.g., they are inhibited by 6.5% NaCl and killed by penicillin G). Note that the hemolytic reaction of group D streptococci is variable: most are α-hemolytic, but some are β-hemolytic, and others are nonhemolytic.

Groups C, E, F, G, H, and K–U streptococci infrequently cause human disease.

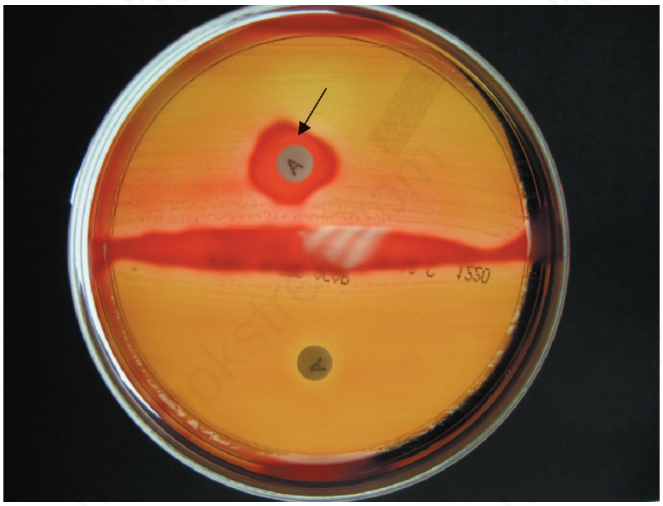

FIGURE 15–13 Bacitracin test—Arrow points to zone of inhibition of growth of group A streptococci (*Streptococcus pyogenes*) caused by bacitracin that has diffused from the disk labeled A. Upper half of blood agar plate shows β-hemolysis caused by group A streptococci, except in the region around the bacitracin disk. Lower half of blood agar plate shows β-hemolysis caused by group B streptococci (*Streptococcus agalactiae*), and there is no zone of inhibition around the bacitracin disk. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

Non–β-Hemolytic Streptococci

Some streptococci produce no hemolysis; others produce α-hemolysis. The principal α-hemolytic organisms are *S. pneumoniae* (pneumococci) and the viridans group of streptococci (e.g., *Streptococcus mitis, Streptococcus sanguinis,* and *Streptococcus mutans*). Pneumococci and viridans streptococci are distinguished in the clinical laboratory by two main criteria: (1) the growth of pneumococci is inhibited by optochin, whereas the growth of viridans streptococci is not inhibited; and (2) colonies of pneumococci dissolve when exposed to bile (bile-soluble), whereas colonies of viridans streptococci do not dissolve.

Viridans streptococci are part of the normal flora of the human pharynx and intermittently reach the bloodstream to cause infective endocarditis. *Streptococcus mutans* synthesizes polysaccharides (dextrans) that are found in dental plaque and lead to dental caries. *Streptococcus intermedius* and *Streptococcus anginosus* (also known as the *S. anginosus-milleri* group) are usually α-hemolytic or nonhemolytic, but some isolates are β-hemolytic. They are found primarily in the mouth and colon.

Peptostreptococci

These grow under anaerobic or microaerophilic conditions and produce variable hemolysis. Peptostreptococci are members of the normal flora of the gut, mouth, and female genital tract and participate in mixed anaerobic infections. The term *mixed anaerobic infections* refers to the fact that these infections are caused by multiple bacteria, some of which are anaerobes and others are facultatives. For example, peptostreptococci and viridans streptococci, both members of the oral flora, are often found in brain abscesses following dental surgery. *Peptostreptococcus magnus* and *Peptostreptococcus anaerobius* are the species frequently isolated from clinical specimens.

Transmission

Most streptococci are part of the normal flora of the human throat, skin, and intestines but produce disease when they gain access to tissues or blood. Viridans streptococci and *S. pneumoniae* are found chiefly in the **oropharynx;** *S. pyogenes* is found on the **skin** and in the oropharynx in small numbers; *S. agalactiae* occurs in the **vagina** and colon; and both the enterococci and anaerobic streptococci are located in the **colon.**

Pathogenesis

Group A streptococci (*S. pyogenes*) cause disease by three mechanisms: (1) **pyogenic inflammation,** which is induced locally at the site of the organisms in tissue; (2) **exotoxin production,** which can cause widespread systemic symptoms in areas of the body where there are no organisms; and (3) **immunologic,** which occurs when antibody against a component of the organism cross-reacts with normal tissue or forms immune complexes that damage normal tissue (see the section on poststreptococcal diseases later in the chapter). The immunologic reactions cause inflammation (e.g., the inflamed joints of rheumatic fever), but there are no organisms in the lesions (Table 15–4).

The M protein of *S. pyogenes* is its most important antiphagocytic factor, but its capsule, composed of hyaluronic

TABLE 15–4 Important Features of Pathogenesis by Streptococci

Organism	Type of Pathogenesis	Typical Disease	Main Site of Disease (D), Colonization (C), or Normal Flora (NF)
S. pyogenes (group A)	1. Pyogenic		
	a. Local	Impetigo, cellulitis	Skin (D)
		Pharyngitis	Throat (D)
	b. Disseminated	Sepsis	Bloodstream (D)
	2. Toxigenic	Scarlet fever	Skin (D)
		Toxic shock	Many organs (D)
	3. Immune-mediated (poststreptococcal, nonsuppurative)	Rheumatic fever	Heart, joints (D)
		Acute glomerulonephritis	Kidney (D)
S. agalactiae (group B)	Pyogenic	Neonatal sepsis and meningitis	Vagina (C)
E. faecalis (group D)	Pyogenic	Urinary tract infection, endocarditis	Colon (NF)
S. bovis (group D)	Pyogenic	Endocarditis	Colon (NF)
S. pneumoniae	Pyogenic	Pneumonia, otitis media, meningitis	Oropharynx (C)
Viridans streptococci	Pyogenic	Endocarditis	Oropharynx (NF)

acid, is also antiphagocytic. Antibodies are not formed against the capsule because hyaluronic acid is a normal component of the body and humans are tolerant to it.

Group A streptococci produce three important **inflammation-related enzymes:**

(1) **Hyaluronidase** degrades hyaluronic acid, which is the ground substance of subcutaneous tissue. Hyaluronidase is known as **spreading factor** because it facilitates the rapid spread of *S. pyogenes* in skin infections (cellulitis).

(2) **Streptokinase** (fibrinolysin) activates plasminogen to form plasmin, which dissolves fibrin in clots, thrombi, and emboli. It can be used to lyse thrombi in the coronary arteries of heart attack patients.

(3) **DNase** (streptodornase) degrades DNA in exudates or necrotic tissue. Antibody to DNase B develops during pyoderma; this can be used for diagnostic purposes. Streptokinase–streptodornase mixtures applied as a skin test give a positive reaction in most adults, indicating normal cell-mediated immunity.

In addition, group A streptococci produce five important **toxins and hemolysins:**

(1) **Erythrogenic toxin** causes the rash of scarlet fever. Its mechanism of action is similar to that of the TSST of *S. aureus* (i.e., it acts as a superantigen; see *S. aureus,* earlier, and Chapter 58). It is produced only by certain strains of *S. pyogenes* lysogenized by a bacteriophage carrying the gene for the toxin. The injection of a skin test dose of erythrogenic toxin (Dick test) gives a positive result in persons lacking antitoxin (i.e., susceptible persons).

(2) **Streptolysin O** is a hemolysin that is inactivated by oxidation (oxygen-labile). It causes β-hemolysis only when colonies grow under the surface of a blood agar plate. It is antigenic, and antibody to it (ASO) develops after group A streptococcal infections. The titer of ASO antibody can be important in the diagnosis of rheumatic fever.

(3) **Streptolysin S** is a hemolysin that is not inactivated by oxygen (oxygen-stable). It is *not* antigenic but is responsible for β-hemolysis when colonies grow on the surface of a blood agar plate.

(4) **Pyrogenic exotoxin A** is the toxin responsible for most cases of streptococcal **toxic shock syndrome.** It has the same mode of action as does staphylococcal TSST (i.e., it is a superantigen that causes the release of large amounts of cytokines from helper T cells and macrophages; see pages 43 and 510).

(5) **Exotoxin B** is a protease that rapidly destroys tissue and is produced in large amounts by the strains of *S. pyogenes,* the so-called "flesh-eating" streptococci that cause necrotizing fasciitis.

Pathogenesis by group B streptococci (*S. agalactiae*) is based on the ability of the organism to induce an inflammatory response. However, unlike *S. pyogenes,* no cytotoxic enzymes or exotoxins have been described, and there is no evidence for any immunologically induced disease. Group B streptococci have a polysaccharide capsule that is antiphagocytic, and anticapsular antibody is protective.

Pathogenesis by *S. pneumoniae* and the viridans streptococci is uncertain, as no exotoxins or tissue-destructive enzymes have been demonstrated. The main virulence factor of *S. pneumoniae* is its antiphagocytic polysaccharide capsule. Many of the strains of viridans streptococci that cause endocarditis produce a glycocalyx that enables the organism to adhere to the heart valve.

Clinical Findings

Streptococcus pyogenes causes three types of diseases: (1) **pyogenic** diseases such as pharyngitis and cellulitis, (2) **toxigenic** diseases such as scarlet fever and toxic shock syndrome, and (3) **immunologic** diseases such as rheumatic fever and acute glomerulonephritis (AGN). (See next section on poststreptococcal diseases.)

Streptococcus pyogenes (group A streptococcus) is the most common bacterial cause of **pharyngitis** (sore throat). Streptococcal pharyngitis (strep throat) is characterized by throat pain and fever. On examination, an inflamed throat and tonsils, often with a yellowish exudate, are found, accompanied by tender cervical lymph nodes. If untreated, spontaneous recovery often occurs in 10 days, but rheumatic fever may occur (see next section on poststreptococcal diseases). Untreated pharyngitis may extend to the middle ear (otitis media), the sinuses (sinusitis), the mastoids (mastoiditis), or the meninges (meningitis). Continuing inability to swallow may indicate a peritonsillar or retropharyngeal abscess.

If the infecting streptococci produce erythrogenic toxin and the host lacks antitoxin, scarlet fever may result. A "strawberry" tongue is a characteristic lesion seen in scarlet fever. *Streptococcus pyogenes* also causes another toxin-mediated disease, streptococcal toxic shock syndrome, which has clinical findings similar to those of staphylococcal toxic shock syndrome (see page 114). However, streptococcal toxic shock syndrome typically has a recognizable site of pyogenic inflammation and blood cultures are often positive, whereas staphylococcal toxic shock syndrome typically has neither a site of pyogenic inflammation nor positive blood cultures.

Group A streptococci cause **skin and soft tissue infections**, such as cellulitis, erysipelas (Figure 15–14), necrotizing fasciitis (streptococcal gangrene), and impetigo (see Figure 15–3). Impetigo, a form of pyoderma, is a superficial skin infection characterized by "honey-colored" crusted lesions. Lymphangitis can occur, especially on the forearm associated with an infection on the hand.

Group A streptococci also cause endometritis (puerperal fever), a serious infection of pregnant women, and

sepsis. Immune-mediated poststreptococcal AGN can also occur, especially following skin infections caused by certain M protein types of *S. pyogenes*.

Group B streptococci cause **neonatal sepsis** and **meningitis.** The main predisposing factor is prolonged (longer than 18 hours) rupture of the membranes in women who are colonized with the organism. Children born prior to 37 weeks' gestation have a greatly increased risk of disease. Also, children whose mothers lack antibody to group B streptococci and who consequently are born without transplacentally acquired IgG have a high rate of neonatal sepsis caused by this organism. Group B streptococci are an important cause of neonatal pneumonia as well.

Although most group B streptococcal infections are in neonates, this organism also causes such infections as pneumonia, endocarditis, arthritis, cellulitis, and osteomyelitis in adults. Postpartum endometritis also occurs. Diabetes is the main predisposing factor for adult group B streptococcal infections.

Viridans streptococci (e.g., *S. mutans, S. sanguinis, S. salivarius,* and *S. mitis*) are the most common cause of infective **endocarditis.** They enter the bloodstream (bacteremia) from the oropharynx, typically after **dental surgery**. Signs of endocarditis are fever, heart murmur, anemia, and embolic events such as splinter hemorrhages, subconjunctival petechial hemorrhages, and Janeway lesions. The heart murmur is caused by vegetations on the heart valve (see Figure 15–10). It is 100% fatal unless effectively treated with antimicrobial agents. About 10% of endocarditis cases are caused by enterococci, but any organism causing bacteremia may settle on deformed valves. At least three blood cultures are necessary to ensure recovery of the organism in more than 90% of cases.

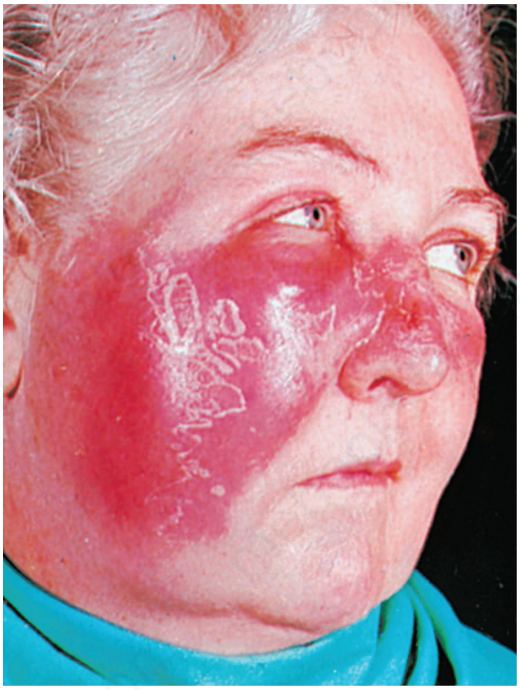

FIGURE 15–14 Erysipelas. Note well-demarcated border of the inflamed area. *Streptococcus pyogenes* is the most common cause of erysipelas. (Reproduced with permission from Longo DL et al (eds): *Harrison's Principles of Internal Medicine.* 18th ed. New York: McGraw-Hill, 2012. Copyright © 2012 by The McGraw-Hill Companies, Inc.)

Viridans streptococci, especially *S. anginosus, S. milleri,* and *S. intermedius,* also cause brain abscesses, often in combination with mouth anaerobes (a mixed aerobic–anaerobic infection). Dental surgery is an important predisposing factor to brain abscess because it provides a portal for the viridans streptococci and the anaerobes in the mouth to enter the bloodstream (bacteremia) and spread to the brain. Viridans streptococci are involved in mixed aerobic–anaerobic infections in other areas of the body as well (e.g., lung abscesses and abdominal abscesses, including liver abscesses).

Enterococci cause **urinary tract infections,** especially in hospitalized patients. Indwelling urinary catheters and urinary tract instrumentation are important predisposing factors. Enterococci also cause endocarditis, particularly in patients who have undergone gastrointestinal or urinary tract surgery or instrumentation. They also cause intra-abdominal and pelvic infections, typically in combination with anaerobes. *Streptococuss bovis,* a nonenterococcal group D streptococcus, causes **endocarditis,** especially in patients with carcinoma of the colon. This association is so strong that patients with *S. bovis,* bacteremia, or endocarditis should be investigated for the presence of colonic carcinoma.

Peptostreptococci are one of the most common bacteria found in brain, lung, abdominal, and pelvic abscesses.

Poststreptococcal (Nonsuppurative) Diseases

These are disorders in which a local infection with group A streptococci is followed weeks later by inflammation in an organ that was *not* infected by the streptococci. The inflammation is caused by an **immunologic** (**antibody**) response to streptococcal M proteins that cross-react with human tissues. Some strains of *S. pyogenes* bearing certain M proteins are nephritogenic and cause AGN, and other strains bearing different M proteins are rheumatogenic and cause acute rheumatic fever. Note that these diseases appear several weeks after the actual infection because that is the length of time it takes to produce sufficient antibodies.

Acute Glomerulonephritis

AGN typically occurs 2 to 3 weeks after skin infection by certain group A streptococcal types in children (e.g., M protein type 49 causes AGN most frequently). AGN is more frequent after skin infections than after pharyngitis. The most striking clinical features are hypertension, edema of the face (especially periorbital edema) and ankles, and

"smoky" urine (due to red cells in the urine). Most patients recover completely. Reinfection with streptococci rarely leads to recurrence of glomerulonephritis.

The disease is initiated by **antigen–antibody complexes on the glomerular basement membrane.** Complement is activated and C5a attracts neutrophils that secrete enzymes that damage the endothelium of the glomerular capillaries. It can be prevented by early eradication of nephritogenic streptococci from skin colonization sites but *not* by administration of penicillin after the onset of symptoms.

Acute Rheumatic Fever

Approximately 2 weeks after a group A streptococcal infection—usually pharyngitis—rheumatic fever, characterized by fever, migratory polyarthritis, and carditis, may develop. The carditis damages myocardial and endocardial tissue, especially the mitral and aortic valves, resulting in vegetations on the valves. Uncontrollable, spasmodic movements of the limbs or face (chorea) may also occur. ASO titers and the erythrocyte sedimentation rate are elevated. Note that group A streptococcal *skin* infections do not cause rheumatic fever. Most cases of pharyngitis caused by group A streptococci occur in children age 5 to 15 years, and hence rheumatic fever occurs in that age group.

Rheumatic fever is due to an **immunologic cross-reaction** between antibodies formed against M proteins of *S. pyogenes* and proteins on the surface of joint, heart and brain tissue. It is an autoimmune disease, greatly exacerbated by recurrence of streptococcal infections. If streptococcal infections are treated within 8 days of onset, rheumatic fever is usually prevented. After a heart-damaging attack of rheumatic fever, reinfection must be prevented by long-term prophylaxis. In the United States, fewer than 0.5% of group A streptococcal infections lead to rheumatic fever, but in developing tropical countries, the rate is higher than 5%.

Laboratory Diagnosis

Microbiologic

Gram-stained smears are useless in streptococcal pharyngitis because viridans streptococci are members of the normal flora and cannot be visually distinguished from the pathogenic *S. pyogenes*. However, stained smears from skin lesions or wounds that reveal streptococci are diagnostic. Cultures of swabs from the pharynx or lesion on blood agar plates show small, translucent β-hemolytic colonies in 18 to 48 hours. If **inhibited by bacitracin** disk, they are likely to be group A streptococci (see Figure 15–13).

Group B streptococci are characterized by their ability to **hydrolyze hippurate** and by the production of a protein that causes enhanced hemolysis on sheep blood agar when combined with β-hemolysin of *S. aureus* (CAMP test). Group D streptococci **hydrolyze esculin in the presence of bile** (i.e., they produce a black pigment on bile-esculin agar). The group D organisms are further subdivided: the enterococci **grow in hypertonic (6.5%) NaCl,** whereas the nonenterococci do not.

Although cultures remain the gold standard for the diagnosis of streptococcal pharyngitis, a problem exists because the results of culturing are not available for at least 18 hours, and it is beneficial to know while the patient is in the office whether antibiotics should be prescribed. For this reason, rapid tests that provide a diagnosis in approximately 10 minutes were developed.

The rapid test detects bacterial antigens in a throat swab specimen. In the test, specific antigens from the group A streptococci are extracted from the throat swab with certain enzymes and are reacted with antibody to these antigens bound to latex particles. Agglutination of the colored latex particles occurs if group A streptococci are present in the throat swab. The specificity of these tests is high, but the sensitivity is low (i.e., false-negative results can occur). If the test result is negative but the clinical suspicion of streptococcal pharyngitis is high, a culture should be done.

A rapid test is also available for the detection of group B streptococci in vaginal and rectal samples. It detects the DNA of the organism, and results can be obtained in approximately 1 hour.

Viridans group streptococci form α-hemolytic colonies on blood agar and must be distinguished from *S. pneumoniae* (pneumococci), which is also α-hemolytic. Viridans group streptococci are resistant to lysis by bile and will grow in the presence of optochin, whereas pneumococci will not. The various viridans group streptococci are classified into species by using a variety of biochemical tests.

Serologic

ASO titers are high soon after group A streptococcal infections. In patients suspected of having rheumatic fever, an **elevated ASO titer** is typically used as evidence of previous infection because throat culture results are often negative at the time the patient presents with rheumatic fever. Titers of anti-DNase B are high in group A streptococcal skin infections and serve as an indicator of previous streptococcal infection in patients suspected of having AGN.

Treatment

Group A streptococcal infections can be treated with either penicillin G or amoxicillin, but neither rheumatic fever nor AGN patients benefit from penicillin treatment *after* the onset of the two diseases. In mild group A streptococcal infections, oral penicillin V can be used. In penicillin-allergic patients, erythromycin or one of its long-acting derivatives (e.g., azithromycin) can be used. However, erythromycin-resistant strains of *S. pyogenes* have emerged that may limit the effectiveness of the macrolide class of drugs in the treatment of streptococcal pharyngitis. Clindamycin can also be used in penicillin-allergic patients. *Streptococcal pyogenes* is not resistant to penicillins.

Endocarditis caused by most viridans streptococci is curable by prolonged penicillin treatment. However, enterococcal endocarditis can be eradicated only by a penicillin or vancomycin combined with an aminoglycoside.

Enterococci resistant to multiple drugs (e.g., penicillins, aminoglycosides, and vancomycin) have emerged. Resistance to vancomycin in enterococci is mediated by a cassette of genes that encode the enzymes that substitute D-lactate for D-alanine in the peptidoglycan. The same set of genes encodes vancomycin resistance in *S. aureus*.

VREs are now an important cause of nosocomial infections; there is no reliable antibiotic therapy for these organisms. At present, two drugs are being used to treat infections caused by VRE: linezolid (Zyvox) and daptomycin (Cubicin).

Nonenterococcal group D streptococci (e.g., *S. bovis*) are not highly resistant and can be treated with penicillin G.

The drug of choice for group B streptococcal infections is either penicillin G or ampicillin. Some strains may require higher doses of penicillin G or a combination of penicillin G and an aminoglycoside to eradicate the organism. Peptostreptococci can be treated with penicillin G.

Prevention

Rheumatic fever can be prevented by prompt treatment of group A streptococcal pharyngitis with penicillin G or oral penicillin V. Prevention of streptococcal infections (usually with benzathine penicillin once each month for several years) in persons who have had rheumatic fever is important to prevent recurrence of the disease. There is no evidence that patients who have had AGN require similar penicillin prophylaxis.

In patients with damaged heart valves who undergo invasive dental procedures, endocarditis caused by viridans streptococci can be prevented by using amoxicillin perioperatively. To avoid unnecessary use of antibiotics, it is recommended to give amoxicillin prophylaxis only to those patients who have the highest risk of severe consequences from endocarditis (e.g., those with prosthetic heart valves or with previous infective endocarditis) and who are undergoing high-risk dental procedures, such as manipulation of gingival tissue. It is no longer recommended that patients undergoing gastrointestinal or genitourinary tract procedures receive prophylaxis.

The incidence of neonatal sepsis caused by group B streptococci can be reduced by a two-pronged approach: (1) All pregnant women at 35 to 37 weeks' gestation should be screened by doing vaginal and rectal cultures. If cultures are positive, then penicillin G (or ampicillin) should be administered intravenously at the time of delivery. (2) If the patient has not had cultures done, then penicillin G (or ampicillin) should be administered intravenously at the time of delivery to women who experience prolonged (longer than 18 hours) rupture of membranes, whose labor begins before 37 weeks' gestation, or who have a fever at the time of labor. If the patient is allergic to penicillin, either cefazolin or vancomycin can be used.

Oral ampicillin given to women who are vaginal carriers of group B streptococci does not eradicate the organism. Rapid screening tests for group B streptococcal antigens in vaginal specimens can be insensitive, and neonates born of antigen-negative women have, nevertheless, had neonatal sepsis. Note, however, that as group B streptococcal infections have declined as a result of these prophylactic measures, neonatal infections caused by *E. coli* have increased.

There are no vaccines available against any of the streptococci except *S. pneumoniae* (see following section).

STREPTOCOCCUS PNEUMONIAE

Diseases

Streptococcus pneumoniae causes pneumonia, bacteremia, meningitis, and infections of the upper respiratory tract such as otitis media, mastoiditis, and sinusitis. Pneumococci are the most common cause of community-acquired pneumonia, meningitis, sepsis in splenectomized individuals, otitis media, and sinusitis. They are a common cause of conjunctivitis, especially in children. Note that *S. pneumoniae* is also known as the pneumococcus (plural, pneumococci).

Important Properties

Pneumococci are gram-positive lancet-shaped cocci arranged in pairs (**diplococci**) or short chains (Figure 15–15). (The term *lancet-shaped* means that the diplococci are oval with somewhat pointed ends rather than being round.) On blood agar, they produce α-hemolysis. In contrast to viridans streptococci, they are lysed by bile or deoxycholate, and their growth is inhibited by optochin (Figure 15–16).

Pneumococci possess **polysaccharide capsules** of more than 85 antigenically distinct types. With type-specific antiserum, capsules swell (**quellung reaction**), and this can be used to identify the type. Capsules are virulence factors (i.e., they interfere with phagocytosis and favor invasiveness). Specific antibody to the capsule opsonizes the organism, facilitates phagocytosis, and promotes resistance. Such antibody develops in humans as a result either of infection (asymptomatic or clinical) or of administration of polysaccharide vaccine. Capsular polysaccharide elicits primarily a β-cell (i.e., T-independent) response.

Another important surface component of *S. pneumoniae* is a teichoic acid in the cell wall called **C-substance** (also known as **C-polysaccharide**). It is medically important not for itself, but because it reacts with a normal serum protein made by the liver called **C-reactive protein** (CRP). CRP is an "acute-phase" protein that is elevated as much as 1000-fold in acute inflammation. CRP is not an antibody (which are γ-globulins) but rather a β-globulin. (Plasma contains

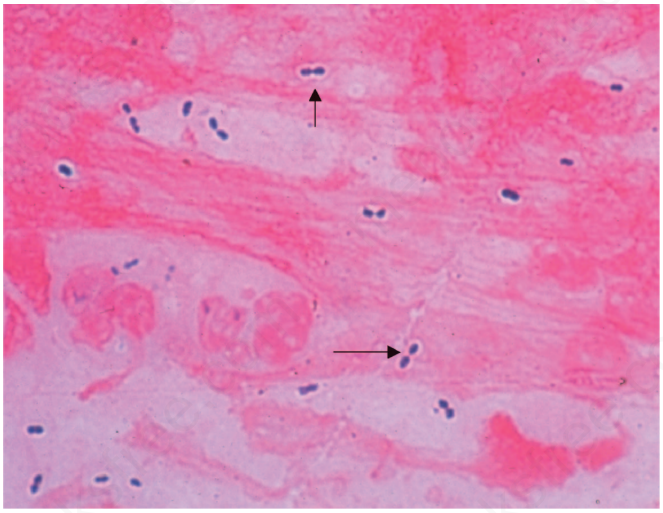

FIGURE 15–15 *Streptococcus pneumoniae*—Gram stain. Arrows point to typical gram-positive diplococci. Note that the clear area around the organism is the capsule. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

α-, β-, and γ-globulins.) Note that CRP is a nonspecific indicator of inflammation and is elevated in response to the presence of many organisms, not just *S. pneumoniae*. Clinically, CRP in human serum is measured in the laboratory by its reaction with the carbohydrate of *S. pneumoniae*. The medical importance of CRP is that an elevated CRP appears to be a better predictor of heart attack risk than an elevated cholesterol level.

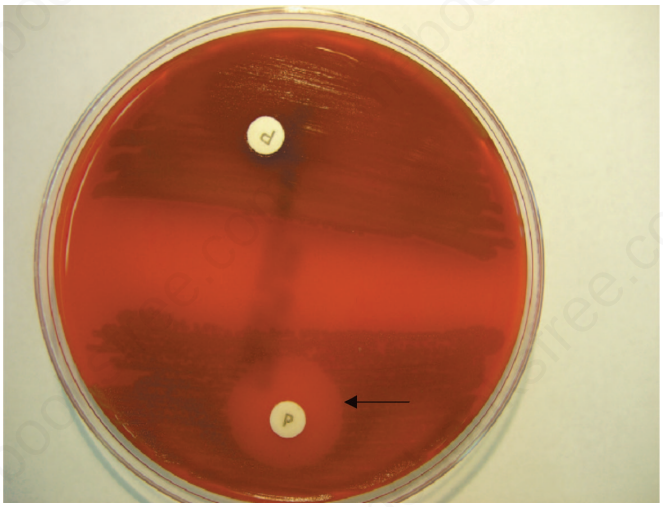

FIGURE 15–16 Optochin test—Arrow points to zone of inhibition of growth of *Streptococcus pneumoniae* caused by optochin that has diffused from the disk labeled P. In the lower half of the blood agar plate, there is α-hemolysis caused by *S. pneumoniae*, except in the region around the optochin disk. The arrow points to the outer limit of the zone of inhibition. Upper half of blood agar plate shows α-hemolysis caused by a viridans streptococcus, and there is no zone of inhibition around the optochin disk. (Used with permission from Professor Shirley Lowe, University of California, San Francisco School of Medicine.)

Transmission

Humans are the natural hosts for pneumococci; there is no animal reservoir. Because a proportion (5%–50%) of the healthy population harbors virulent organisms in the oropharynx, pneumococcal infections are not considered to be communicable. Resistance is high in healthy young people, and disease results most often when predisposing factors (see following discussion) are present.

Pathogenesis

The most important virulence factor is the capsular polysaccharide, and anticapsular antibody is protective. Lipoteichoic acid, which activates complement and induces inflammatory cytokine production, contributes to the inflammatory response and to the septic shock syndrome that occurs in some immunocompromised patients. Pneumolysin, the hemolysin that causes α-hemolysis, may also contribute to pathogenesis.

Pneumococci produce **IgA protease** that enhances the organism's ability to colonize the mucosa of the upper respiratory tract by cleaving IgA. Pneumococci multiply in tissues and cause inflammation. When they reach alveoli, there is outpouring of fluid and red and white blood cells, resulting in consolidation of the lung. During recovery, pneumococci are phagocytized, mononuclear cells ingest debris, and the consolidation resolves.

Factors that lower resistance and predispose persons to pneumococcal infection include (1) alcohol or drug intoxication or other cerebral impairment that can depress the cough reflex and increase aspiration of secretions; (2) abnormality of the respiratory tract (e.g., viral infections), pooling of mucus, bronchial obstruction, and respiratory tract injury caused by irritants (which disturb the integrity and movement of the mucociliary blanket); (3) abnormal circulatory dynamics (e.g., pulmonary congestion and heart failure); (4) **splenectomy;** and (5) certain chronic diseases such as sickle cell anemia and nephrosis. Patients with sickle cell anemia auto-infarct their spleen, become functionally asplenic, and are predisposed to pneumococcal sepsis. Trauma to the head that causes **leakage of spinal fluid** through the nose predisposes to pneumococcal meningitis.

Clinical Findings

Pneumonia often begins with a sudden chill, fever, cough, and pleuritic pain. Sputum is a red or brown "rusty" color. Bacteremia occurs in 15% to 25% of cases. Spontaneous recovery may begin in 5 to 10 days and is accompanied by development of anticapsular antibodies. Pneumococci are a prominent cause of otitis media, sinusitis, mastoiditis, conjunctivitis, purulent bronchitis, pericarditis, bacterial meningitis, and sepsis. Pneumococci are the leading cause of sepsis in patients without a functional spleen.

Laboratory Diagnosis

In sputum, pneumococci are seen as lancet-shaped gram-positive diplococci in Gram-stained smears (see Figure 15–15). They can also be detected by using the quellung reaction with multitype antiserum. On blood agar, pneumococci form small α-**hemolytic** colonies. The colonies are **bile-soluble** (i.e., are lysed by bile), and growth is **inhibited by optochin** (see Figure 15–16).

Blood cultures are positive in 15% to 25% of pneumococcal infections. Culture of cerebrospinal fluid is usually positive in meningitis. Rapid diagnosis of pneumococcal meningitis can be made by detecting its capsular polysaccharide in spinal fluid using the latex agglutination test. A rapid test that detects urinary antigen is also available for the diagnosis of pneumococcal pneumonia and bacteremia. The urinary antigen is the C polysaccharide (also known as the C substance), *not* the capsular polysaccharide. Because of the increasing numbers of strains resistant to penicillin, antibiotic sensitivity tests must be done on organisms isolated from serious infections.

Treatment

Most pneumococci are susceptible to penicillins and erythromycin, although significant resistance to penicillins has emerged (see next paragraph). In severe pneumococcal infections, penicillin G is the drug of choice, whereas in mild pneumococcal infections, oral penicillin V can be used. A fluoroquinolone with good antipneumococcal activity, such as levofloxacin, can also be used. In penicillin-allergic patients, erythromycin or one of its long-acting derivatives (e.g., azithromycin) can be used.

In the United States, about 25% of isolates exhibit low-level resistance to penicillin, primarily as a result of changes in penicillin-binding proteins. An increasing percentage of isolates, ranging from 15% to 35% depending on location, show **high-level resistance**, which is attributed to multiple **changes in penicillin-binding proteins**. They do *not* produce β-lactamase. Vancomycin is the drug of choice for the penicillin-resistant pneumococci, especially for severely ill patients. Ceftriaxone or levofloxacin can be used for less severely ill patients. However, strains of pneumococci tolerant to vancomycin have emerged. (Tolerance to antibiotics is described on pages 71 and 90.) Strains of pneumococci resistant to multiple drugs have also emerged.

Prevention

Despite the efficacy of antimicrobial drug treatment, the mortality rate of pneumococcal infections is high in immunocompromised (especially splenectomized) patients and children under the age of 5 years. Such persons should be immunized with the **13-valent pneumococcal conjugate vaccine** (Prevnar 13). The immunogen in this vaccine is the pneumococcal polysaccharide of the 13 most prevalent serotypes conjugated (coupled) to a carrier protein (diphtheria toxoid). The unconjugated 23-valent pneumococcal vaccine (Pneumovax 23) should be given to healthy individuals age 50 years or older.

These vaccines are safe and effective and provide long-lasting (at least 5 years) protection. Immunization of *children* reduces the incidence of pneumococcal disease in *adults* because children are the main source of the organism for adults and immunization reduces the carrier rate in children.

A booster dose is recommended for (1) people older than 65 years who received the vaccine more than 5 years ago and who were younger than 65 years when they received the vaccine, and (2) people between the ages of 2 and 64 years who are asplenic, infected with human immunodeficiency virus (HIV), receiving cancer chemotherapy, or receiving immunosuppressive drugs to prevent transplant rejection.

A potential problem regarding the use of the pneumococcal vaccine is that of **serotype replacement.** Will the vaccine reduce the incidence of disease caused by the serotypes in the vaccine but not the overall incidence of pneumococcal disease because other serotypes that are not in the vaccine will now cause disease? In fact, an increase in invasive pneumococcal disease caused by serotype 19A, which was not in the previously used 7-valent vaccine, occurred. This led to the production of the current conjugate vaccine containing 13 serotypes, including 19A.

SELF-ASSESSMENT QUESTIONS

1. You're in the clinical laboratory looking at a Gram stain when the laboratory technician comes up to you and says, "I think your patient has Staph epi [short for *Staphylococcus epidermidis*] bacteremia." Which one of the following sets of results did the tech find with the organism recovered from the blood culture?
   (A) Gram-positive cocci in chains, catalase-positive, coagulase-positive
   (B) Gram-positive cocci in chains, catalase-negative, coagulase-negative
   (C) Gram-positive cocci in clusters, catalase-positive, coagulase-negative
   (D) Gram-positive cocci in clusters, catalase-negative, coagulase-positive
   (E) Gram-positive diplococci, catalase-negative, coagulase-positive
2. Superantigen production by *Staphylococcus aureus* is involved in the pathogenesis of which one of the following diseases?
   (A) Impetigo
   (B) Osteomyelitis
   (C) Scalded skin syndrome
   (D) Septicemia
   (E) Toxic shock syndrome
3. Which one of the following is the virulence factor produced by *Staphylococcus aureus* that prevents the activation of complement and thereby reduces opsonization by C3b?
   (A) Catalase
   (B) Coagulase

(C) Endotoxin
(D) Protein A
(E) Teichoic acid

4. The main reason why methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to methicillin and nafcillin is:
(A) they produce β-lactamase that degrades the antibiotics.
(B) they have altered penicillin-binding proteins that have reduced binding of the antibiotics.
(C) they have mutant porin proteins that prevent the antibiotics from entering the bacteria.
(D) they have plasmid-encoded export proteins that remove the drug from the bacteria.

5. A pore-forming exotoxin produced by *Staphylococcus aureus* that kills cells and is important in the severe, rapidly spreading necrotizing lesions caused by MRSA strains is:
(A) coagulase.
(B) enterotoxin.
(C) exfoliatin.
(D) P-V leukocidin.
(E) staphyloxanthin.

6. Of the following antibiotics, which one is the most appropriate to treat a severe necrotizing skin infection caused by an MRSA strain of *Staphylococcus aureus*?
(A) Amoxicillin
(B) Ceftriaxone
(C) Ciprofloxacin
(D) Gentamicin
(E) Vancomycin

7. An outbreak of serious pneumococcal pneumonia and sepsis among inmates in an overcrowded prison has occurred. Laboratory analysis determined that one serotype was involved. The prison physician said that the pneumococcal vaccine might have limited the outbreak. Which one of the following structures of the pneumococcus is responsible for determining the serotype and is also the immunogen in the vaccine?
(A) Capsule
(B) Flagellar protein
(C) O antigen
(D) Peptidoglycan
(E) Pilus protein

8. Which one of the following best describes the pathogenesis of rheumatic fever?
(A) An exotoxin produced by *Streptococcus pyogenes* that acts as a superantigen damages cardiac muscle.
(B) An exotoxin produced by *Streptococcus pyogenes* that ADP-ribosylates a G protein damages joint tissue.
(C) Antibody to the capsular polysaccharide of *Streptococcus pyogenes* cross-reacts with joint tissue and damages it.
(D) Antibody to the M protein of *Streptococcus pyogenes* cross-reacts with cardiac muscle and damages it.
(E) Endotoxin produced by *Streptococcus pyogenes* activates macrophages to release cytokines that damage cardiac muscle.

9. Which one of following laboratory tests is the most appropriate to distinguish *Streptococcus pyogenes* from other β-hemolytic streptococci?
(A) Ability to grow in 6.5% NaCl
(B) Activation of C-reactive protein
(C) Hydrolysis of esculin in the presence of bile
(D) Inhibition by bacitracin
(E) Inhibition by optochin

10. Infections by which one of the following bacteria are typically treated with penicillins such as amoxicillin, because they exhibit neither low-level resistance nor high-level resistance and synergy with an aminoglycoside is not required in order for penicillins to be effective?
(A) *Enterococcus faecalis*
(B) *Staphylococcus aureus*
(C) *Staphylococcus epidermidis*
(D) *Streptococcus pneumoniae*
(E) *Streptococcus pyogenes*

11. Your patient in the emergency room has a 5-cm ulcer on her leg that is surrounded by a red, warm, and tender area of inflammation. You do a Gram stain on pus from the ulcer and see gram-positive cocci in chains. Culture of the pus grows small β-hemolytic colonies that are catalase-negative and are inhibited by bacitracin. These results indicate that the organism causing her lesion is most likely:
(A) *Enterococcus faecalis.*
(B) *Staphylococcus aureus.*
(C) *Streptococcus agalactiae.*
(D) *Streptococcus pneumoniae.*
(E) *Streptococcus pyogenes.*

12. The Jones family of four had a delicious picnic lunch last Sunday. It was a warm day, and the food sat in the sun for several hours. Alas, 3 hours later, everyone came down with vomiting and nonbloody diarrhea. In the emergency room, it was found that Mrs. Jones, who prepared the food, had a paronychia on her thumb. Which one of the following is the most likely causative organism?
(A) *Enterococcus faecalis*
(B) *Staphylococcus aureus*
(C) *Staphylococcus epidermidis*
(D) *Streptococcus agalactiae*
(E) *Streptococcus pyogenes*

13. A 20-year-old sexually active woman reports dysuria and other symptoms of a urinary tract infection. Gram stain of the urine reveals gram-positive cocci. Which one of the following sets of bacteria is most likely to cause this infection?
(A) *Staphylococcus aureus* and *Streptococcus pyogenes*
(B) *Staphylococcus saprophyticus* and *Enterococcus faecalis*
(C) *Streptococcus agalactiae* and *Staphylococcus epidermidis*
(D) *Streptococcus pneumoniae* and *Enterococcus faecalis*
(E) *Streptococcus pyogenes* and *Streptococcus pneumoniae*

14. Your patient is a 2-week-old infant who was well until 2 days ago, when she stopped feeding and became irritable. She now has a fever to 38°C, developed a petechial rash all over her body, and is very difficult to arouse. In the emergency room, a blood culture and a spinal tap were done. Gram stain of the spinal fluid showed gram-positive cocci in chains. Culture of the spinal fluid on blood agar revealed β-hemolytic colonies that grew in the presence of bacitracin and hydrolyzed hippurate. Which one of the following is the most likely causative organism?
(A) *Staphylococcus aureus*
(B) *Streptococcus agalactiae*
(C) *Streptococcus mutans*
(D) *Streptococcus pneumoniae*
(E) *Streptococcus pyogenes*

15. Your patient is a 50-year-old woman who has a community-acquired pneumonia caused by *Streptococcus pneumoniae.* Antibiotic susceptibility tests reveal an MIC of less than 0.1 mg/mL

to penicillin G. Which one of the following is the best antibiotic to treat the infection?

(A) Clindamycin
(B) Gentamicin
(C) Metronidazole or doxycycline
(D) Penicillin G or levofloxacin
(E) Vancomycin

16. Your patient is a 70-year-old man with endocarditis caused by *Enterococcus faecalis*. Which one of the following is the best combination of antibiotics to treat the infection?

(A) Azithromycin and trimethoprim-sulfamethoxazole
(B) Chloramphenicol and rifampin
(C) Doxycycline and levofloxacin
(D) Metronidazole and clindamycin
(E) Penicillin G and gentamicin

ANSWERS

1. **(C)**
2. **(E)**
3. **(D)**
4. **(B)**
5. **(D)**
6. **(E)**
7. **(A)**
8. **(D)**
9. **(D)**
10. **(E)**
11. **(E)**
12. **(B)**
13. **(B)**
14. **(B)**
15. **(D)**
16. **(E)**

SUMMARIES OF ORGANISMS

Brief summaries of the organisms described in this chapter begin on page 653. Please consult these summaries for a rapid review of the essential material.

PRACTICE QUESTIONS: USMLE & COURSE EXAMINATIONS

Questions on the topics discussed in this chapter can be found in the Clinical Bacteriology section of Part XIII: USMLE (National Board) Practice Questions starting on page 713. Also see Part XIV: USMLE (National Board) Practice Examination starting on page 751.