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20-valent pneumococcal conjugate vaccine, PREVNAR 20 (Pfizer). Both vaccines are now also licensed for infant immunization and are likely to gradually replace PCV10 and PCV13. The additional serotypes in the new vaccines account for a variable fraction of the residual IPD in children (additional 15–45%) and adults (additional 11–33%) for PCV15 and PCV20, respectively, in countries where PCV13 coverage is high. For adults the United States Advisory Committee on Immuni zation Practices (ACIP) now recommends PCV20 instead of PPSV23 for all persons ≥65 years of age and for those 2–64 years of age who have underlying medical conditions that put them at increased risk for pneumococcal disease or, if infected, disease of increased severity (Table 151-1; see also www.cdc.gov/vaccines/schedules). United States

recommendations for PPSV23 are now limited to sequential use in the above age groups receiving the PCV15 vaccine. The introduction of PCV in high-income settings has resulted in a

> 90% reduction in vaccine-serotype IPD among the whole population. This decline has been noted not only in those age groups immunized but also in adults and is attributable to the near elimination of vaccine-

serotype nasopharyngeal colonization in immunized infants, which reduces spread to adults. This protection of unimmunized community members through vaccination of a subset of the community is termed the indirect effect. Increases in colonization with—and concomitantly in disease due to—non-vaccine-serotype strains (i.e., replacement colonization and disease) have been seen. The scale of replacement disease has varied geographically with the impact eroding vaccine impact significantly in the elderly in the United Kingdom while having relatively little impact in the United States (see “Epidemiology,” above). Since vaccine-serotype strains are more commonly resistant to anti biotics than are non-vaccine serotypes, use of PCV has also resulted in substantial declines in the proportion and absolute rates of drugresistant pneumococcal disease. The ACIP recommendations for the use of conjugate vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. PCV has been shown to prevent pneumococcal infection in HIV-infected adults. Other Prevention Strategies Pneumococcal disease can be averted through the prevention of illnesses that predispose individu als to pneumococcal infections. Relevant measures include smoking cessation and influenza vaccination, as well as improved management and control

of diabetes, HIV infection, heart disease, and lung disease. Finally, the reduction of antibiotic misuse is a strategy for the preven tion of pneumococcal disease in that antimicrobial resistance directly and indirectly perpetuates organism transmission and disease in the community. ■ ■GLOBAL HEALTH In 2015, pneumococcal infections were estimated to have caused ~317,000 annual deaths worldwide among children 1–59 months of age, accounting for 9.7% of the 3.2 million all-cause deaths and 38% of all pneumonia deaths in this age group. Updated estimates of residual pneumococcal disease burden since the widespread introduction of PCV have not been published. Reliable estimates of adult cases and deaths globally are more difficult to establish because of limited data from parts of the world where most disease occurs. Rates of pneumo coccal disease and mortality vary substantially across geographic set tings, with the highest rates in selected countries of sub-Saharan Africa and southern Asia, where risk factors for pneumococcal disease— including HIV infection, lack of breast feeding of infants and children, malnutrition, sickle cell disease, and limited access to medical care— are prevalent. Serotypes causing disease exhibit some heterogeneity across geographic settings, but a small number of serotypes universally account for the preponderance of disease in the absence of vaccina tion; accordingly, vaccine development and vaccination programs are globally relevant. Reductions in disease from pneumococcal infections are anchored in prevention through the inclusion of pneumococcal vaccines in infant immunization programs, timely assessment and appropriate treatment of persons with pneumococcal infections, and reduction of risk factors for pneumococcal disease. The use of vaccines for the prevention of adult pneumococcal disease, particularly among

the elderly, is currently implemented in high-income countries, with virtually no use in low-income countries where most cases of disease exist.

■ ■FURTHER READING Krone CL et al: Immunosenescence and pneumococcal disease: An imbalance in host–pathogen interactions. Lancet Respir Med 2:141, 2014. Lees JA et al: Fast and flexible bacterial genomic epidemiology with PopPUNK. Genome Res 29:304, 2019. Mackenzie GA et al: The impact of the introduction of pneumococcal conjugate vaccination in invasive pneumococcal disease and pneumonia in The Gambia: 10 years of population-based surveillance. Lancet Infect Dis 21:1293, 2021. Subramanian K et al: Pneumolysin binds to the mannose recep tor C type 1 (MRC-1) leading to anti-inflammatory responses and enhanced pneumococcal survival. Nat Microbiol 4:62, 2019. Van Der Poll T, Opal SM: Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet 374:1543, 2009. ■ ■WEBSITES American Academy of Pediatrics: Red Book: The report of the Committee on Infectious Diseases. Available at: aapredbook.aap publications.org. Cochrane: Corticosteroids for Bacterial Meningitis. Available at: www. cochrane.org/CD004405/ARI_corticosteroids-bacterial-meningitis. U.S. Department of Health and Human Services: Antibiotic Resistance Threats in the United States 2019. Available at: www.cdc. gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. World Health Organization: Summary of WHO Position Paper CHAPTER 152 on Pneumococcal conjugate vaccines in infants and children under 5 years of age, February 2019. Available at: www.who.int/ publications/i/item/10665-310968. Staphylococcal Infections Franklin D. Lowy, Anne-Catrin Uhlemann

Staphylococcal Infections Staphylococcus aureus, the most virulent of the many (≥40) staphylococ cal species, has demonstrated its versatility by remaining a major cause of morbidity and mortality worldwide despite the availability of numerous effective antistaphylococcal antibiotics. S. aureus is

a pluripotent pathogen, causing disease through both toxin- and non-toxin-mediated mecha nisms. It is responsible for numerous nosocomial and community-based infections that range from relatively minor skin and soft tissue infections (SSTIs) to life-threatening systemic infections. The “other” staphylococci, coagulase-negative staphylococci, are less virulent than S. aureus but remain important pathogens in select set tings, such as infections involving prosthetic devices. MICROBIOLOGY AND TAXONOMY Staphylococci, gram-positive cocci in the family Micrococcaceae, form grapelike clusters on Gram’s stain (Fig. 152-1). These organisms (~1 μm in diameter) are catalase-positive (unlike streptococcal spe cies), nonmotile, aerobic, and facultatively anaerobic. They are capable of prolonged survival on environmental surfaces under varying condi tions. Some species have a relatively broad host range, including mam mals and birds, whereas the host range for others is quite narrow—i.e., limited to one or two closely related animals. S. aureus is generally distinguished from other staphylococcal spe cies by coagulase production, a surface enzyme that converts fibrinogen to fibrin. However, several of the “coagulase-negative staphylococci,”

FIGURE 152-1 Gram’s stain of S. aureus in a sputum sample, illustrating staphylococcal clusters. (From ASM MicrobeLibrary.org. © Pfizer, Inc.) including S. pseudintermedius and S. argenteus, are coagulase-positive. As a result, description of these other staphylococci as non–S. aureus staphylococci (NSaS) is more accurate. S. aureus ferments mannitol, is positive for protein A, and produces DNAse. On blood agar plates, S. aureus forms golden β-hemolytic colo nies; in contrast, most NSaS form small, white nonhemolytic colonies. Latex kits that detect both protein A and clumping factor can distin guish S. aureus from most other staphylococcal species. Point-of-care tests targeting these two proteins also are used for the rapid detection of staphylococcal colonization. Newer methods such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDITOF) are increasingly being used for staphylococcal speciation. PART 5 Infectious Diseases Determining whether multiple staphylococcal isolates from differ ent patients are the same or different is often relevant when there is concern that a nosocomial outbreak of staphylococcal infections is due to a common point source (e.g., a contaminated medical instrument). Molecular typing methods, such as pulsed-field gel electrophoresis and sequence-based techniques (e.g., staphylococcal protein A [SpA] typing), have been used for this purpose. More recently, whole-genome sequencing has emerged as the gold standard for discrimination among different isolates. S. AUREUS INFECTIONS ■ ■EPIDEMIOLOGY S. aureus is both a commensal and an opportunistic pathogen. Approx imately 20–40% of healthy persons are colonized with S. aureus, with a smaller percentage (~10%) persistently colonized with the same strain. The rate of colonization is elevated among type 1 diabetics, HIV-infected patients, patients undergoing hemodialysis, injection drug users, and individuals with damaged skin. The anterior nares and oropharynx are frequent sites of human colonization, although the skin (especially when damaged), axilla, vagina, and perineum also are often colonized. These colonization sites serve as potential reservoirs for future infections. Most individuals who develop S. aureus infections become infected with a strain that is already a part of their own commensal flora. Breaches of the skin or mucosal membrane allow S. aureus to initiate infection. Person-to-person transmission of S. aureus also occurs, most frequently from direct personal contact with an infected body site. Spread of staphylococci in aerosols of respiratory or nasal secretions from heavily colonized individuals, although rare, has been reported. Some diseases increase the risk of S. aureus infection. Diabetes, for example, combines an increased rate of S. aureus colonization and the use of injectable insulin with the possibility of impaired leuko cyte function. Individuals with congenital or acquired qualitative or quantitative defects of polymorphonuclear leukocytes (PMNs) are at increased risk of

S. aureus infections; this group includes neutropenic patients (e.g., those receiving chemotherapeutic agents), those with

chronic granulomatous disease, and those with autosomal dominant hyperimmunoglobulin E (Job syndrome) or Chédiak-Higashi syn drome. Other groups at risk include individuals with end-stage renal disease, HIV infection, skin abnormalities, or prosthetic devices. S. aureus is a leading cause of health care–associated infections (Chap. 147). It is the most common cause of surgical wound infections and is second only to NSaS as a cause of primary bacteremia. These iso lates are often resistant to multiple antibiotics; thus, available therapeutic options may be limited. In the community, S. aureus remains an important cause of SSTIs, respiratory infections, and, especially among injection drug users, infective endocarditis. The increasing use of home infusion therapy also poses a risk of community-acquired staphylococcal infections. In the past three decades, there has been a dramatic change in the epidemiology of infections due to methicillin-resistant S. aureus (MRSA). In addition to its major role as a nosocomial pathogen, MRSA has become an established community-based pathogen. Numerous outbreaks of community-associated MRSA (CA-MRSA) infections have been reported in both rural and urban settings in widely separated regions throughout the world. This trend appears to be due in part to the dramatic increase in MRSA colonization found in the community in different parts of the world. Outbreaks of CA-MRSA infections have occurred among such diverse groups as children, prisoners, athletes, Native Americans, and drug users. Risk factors common to these outbreaks include poor hygienic conditions, close contact, contaminated material, and dam aged skin. In some geographic regions of the world, the infections have been caused by a single CA-MRSA strain, while in others, a variety of CA-MRSA strains have been responsible. In the United States, strain sequence type 8 (PFGE type USA300) has been the predominant clone (Fig. 152-2). Although most infections caused by these strains have involved the skin and soft tissue, 5–10% have been invasive and poten tially life-threatening. CA-MRSA strains have also been responsible for an increasing number of nosocomial infections. Of concern has been the enhanced capacity of CA-MRSA to cause disease in immunocom petent individuals. ■ ■PATHOGENESIS General Concepts S. aureus is a pyogenic pathogen known for its capacity to induce abscess formation at both local and distant sites (i.e., metastatic infections). This classic pathologic response to S. aureus defines the framework within which infections will progress. The bac teria elicit an inflammatory response characterized by an initial intense infiltration of PMNs and a subsequent infiltration of macrophages and fibroblasts. Either the host cellular response (including the deposition of fibrin and collagen) contains the infection with the formation of a fibrinous capsule, or infection spreads to the adjoining tissue or into the bloodstream. In toxin-mediated staphylococcal disease, infection is not invari ably present. For example, in staphylococcal food poisoning, once the heat-stable enterotoxin has been released into food, symptoms can develop in the absence of viable bacteria. In staphylococcal toxic shock syndrome (TSS), conditions allowing toxin elaboration at colonization sites (e.g., the presence of a superabsorbent tampon) suffice for initia tion of clinical illness. The S. aureus Genome The complete genomes of S. aureus strains are now readily available. Among the interesting revela tions are (1) the high degree of nucleotide sequence similarity of the core genomes of different strains; (2) the acquisition of a relatively large amount of genetic information by horizontal transfer from other bacterial species; and (3) the presence of unique “pathogenicity” or “genomic” islands—mobile genetic elements that contain clusters of enterotoxin and exotoxin genes and/or antimicrobial resistance deter minants. Among the genes in these islands is mecA, the gene respon sible for methicillin resistance. Methicillin resistance–containing islands have been

designated staphylococcal cassette chromosome mec (SCCmec). There are different SCCmec types that range in size from ~20 to 60 kb. Among the more common SCCmec types, types 1–3 are

FIGURE 152-2 Global distribution of community-associated MRSA. Dotted lines indicate possible route of dissemination. Estimates of the areas are shown where infection with the main strains—i.e., ST1 (green), ST8 (red), ST30 (blue), and ST80 (gray hatched)—have been reported. +, Panton-Valentine leukocidin (PVL)-positive strains; –, PVL-negative strains; ±, PVL-positive and -negative strains. (Reproduced with permission from FR DeLeo, M Otto, BN Kreiswirth, HF Chambers: Community-associated methicillin-resistant Staphylococcus aureus. Lancet 375:1557, 2010.) traditionally associated with nosocomial MRSA isolates, whereas types 4–6 have been associated with epidemic CA-MRSA strains. A relatively limited number of MRSA clones have been responsible for most community- and hospital-associated infections worldwide. A comparison of these strains with those from earlier outbreaks (e.g., the phage 80/81 strains from the 1950s) has revealed preservation of much of the nucleotide sequence over time. This observation suggests that these strains possess determinants that facilitate survival and spread. Regulation of Virulence Gene Expression In both toxinmediated and non-toxin-mediated diseases due to S. aureus, the expression of virulence determinants associated with infection depends on a series of regulatory genes (e.g., accessory gene regulator [agr] and staphylococcal accessory regulator [sar]) that coordinately control the expression of many virulence genes. The regulatory gene agr is part of a quorum-sensing signal transduction pathway that senses and responds to bacterial density. Staphylococcal surface pro teins are synthesized during the bacterial exponential growth phase in vitro. In contrast, many secreted proteins, such as α toxin, the entero toxins, and assorted enzymes, are released during the post–exponential growth phase in response to transcription of the effector molecule of agr, RNAIII. These regulatory genes appear to serve a similar function in vivo. Successful invasion requires the sequential expression of these different bacterial elements. Bacterial adhesins are needed to initiate coloniza tion of host tissue surfaces. The subsequent release of various enzymes enables the colony to obtain nutritional support and permits bacteria to spread to adjacent tissues. Studies with strains in which these regu latory genes are inactivated show reduced virulence in several animal models of S. aureus infection. Pathogenesis of Invasive S. aureus Infection Staphylococci are opportunists. For these organisms to invade the host and cause infection, some or all of the following steps are necessary: contamina tion and colonization of host tissue surfaces, breach of cutaneous or mucosal barriers, establishment of a localized infection, invasion, eva sion of the host response, and metastatic spread. Colonizing strains or strains transferred from other exposures are introduced into damaged skin, a wound, or the bloodstream. Recurrences of S. aureus infections are common, apparently because of the capacity of these pathogens to

CHAPTER 152 persist in a quiescent state in various tissues, and then to cause recru descent infections when suitable conditions arise. S. AUREUS COLONIZATION OF BODY SURFACES The anterior nares and oropharynx are primary sites of staphylococcal colonization. In the nares, colonization appears to involve the attachment of S. aureus to keratinized epithelial cells. Other factors that contribute to colo nization include the influence of other resident nasal flora and their bacterial density, host factors, and nasal mucosal damage (e.g., that resulting from inhalational drug use). Other colonized body sites, such as damaged skin, the groin, and the oropharynx, may be particularly important reservoirs for CA-MRSA strains. Staphylococcal Infections INOCULATION AND COLONIZATION OF TISSUE SURFACES Staphylo cocci may be introduced into tissue as a result

of minor abrasions (e.g., mosquito bites), administration of medications such as insulin, or estab lishment of IV access with catheters. After introduction into a tissue site, bacteria replicate and colonize the host tissue surface. A family of struc turally related S. aureus surface proteins referred to as MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) play an important role as mediators of adherence to these different sites. By adhering to exposed matrix molecules (e.g., fibrinogen, collagen, fibronectin), MSCRAMMs, such as clumping factor and collagen-binding protein, enable the bacteria to colonize different host tissue surfaces; these proteins contribute to the pathogenesis of invasive infections such as endocarditis and septic arthritis by facilitating the adherence of S. aureus to surfaces with exposed fibrinogen or collagen. Although NSaS are classically known for their ability to elaborate biofilms and to colonize prosthetic devices, S. aureus also possesses the genes responsible for biofilm formation, such as the intercellular adhe sion (ica) locus. Binding to these devices occurs in a stepwise fashion, involving staphylococcal adherence to serum constituents that have coated the device surface and subsequent biofilm elaboration. S. aureus is thus a frequent cause of biomedical device–related infections. INVASION After colonization, staphylococci replicate at the initial site of infection, elaborating enzymes that include serine proteases, hyaluronidases, thermonucleases, and lipases. These enzymes facilitate bacterial survival and local spread across tissue surfaces. The lipases may facilitate survival in lipid-rich areas such as the hair follicles, where S. aureus infections are often initiated.

Constitutional findings may result from either localized or systemic infections. The staphylococcal cell wall—consisting of alternating N-acetyl muramic acid and N-acetyl glucosamine units in combination with an additional cell wall component, lipoteichoic acid—can initiate an inflammatory response that includes the sepsis syndrome. Staphy lococcal alpha (α) toxin is a critical staphylococcal toxin. It causes pore formation in various eukaryotic cells and can also initiate an inflam matory response with findings suggestive of sepsis. The S. aureus toxin Panton-Valentine leukocidin is cytolytic to PMNs, macrophages, and monocytes. Strains elaborating this toxin have been epidemiologically linked with cutaneous and more serious infections (i.e., pneumonia) caused by strains of CA-MRSA.

EVASION OF HOST DEFENSE MECHANISMS Staphylococci have many host immune evasion strategies that are crucial to their survival. They possess an antiphagocytic polysaccharide microcapsule. Most human S. aureus infections are due to strains with capsular types 5 and 8. The zwitterionic (both negatively and positively charged) S. aureus capsule also plays a critical role in the induction of abscess formation. Protein A, an MSCRAMM unique to S. aureus, acts as an Fc receptor, binding the Fc portion of IgG subclasses 1, 2, and 4 and preventing opsonophagocytosis by PMNs. Both chemotaxis inhibitory protein of staphylococci (CHIPS, a secreted protein) and extracellular adherence protein (EAP, a surface protein) interfere with PMN migration to sites of infection. There are several cytolytic toxins, including α toxin and Panton-Valentine toxin, that are secreted by staphylococci that cause lysis of different host cells and contribute to host tissue damage. An additional potential mechanism of S. aureus evasion is its capac ity for intracellular survival. Both professional and nonprofessional phagocytes internalize staphylococci. Internalization by these cells may provide a sanctuary that protects bacteria against the host’s defenses. This phenomenon appears to be especially relevant for hepatic Kupffer cells during staphylococcal bacteremias. The intracellular environment favors the phenotypic expression of S. aureus small-colony variants, which are found in patients receiving antimicrobial therapy (e.g., with

aminoglycosides) and in those with cystic fibrosis or osteomyelitis. These variants, whether intra- or extracellular, may facilitate prolonged staphylococcal survival in different tissue sites and enhance the likeli hood of recurrences. Finally, S. aureus can survive within PMNs and may use these cells to spread and seed other tissue sites. PART 5 Infectious Diseases PATHOGENESIS OF COMMUNITY-ACQUIRED MRSA INFECTIONS A number of specific virulence determinants contribute to the patho genesis of CA-MRSA infections. A strong epidemiologic association links the presence of the gene for the Panton-Valentine leukocidin with SSTIs and with necrotizing postinfluenza pneumonia. Other determinants that play a role in the pathogenesis of these infections and contribute to the unique virulence of these clones include the arginine catabolic mobile element (ACME), a cluster of unique genes that may facilitate evasion of host defense mechanisms; phenol-soluble modulins, a family of cytolytic peptides; and α toxin. Host Response to S. aureus Infection The primary host response to S. aureus infection is the recruitment of PMNs. These cells are attracted to infection sites by bacterial components such as formylated peptides or peptidoglycan as well as by the cytokines tumor necrosis factor (TNF) and interleukins (ILs) 1 and 6, which are released by activated macrophages and endothelial cells. Although most individuals have antibodies to staphylococci, it is not clear that antibody levels are qualitatively or quantitatively sufficient to protect against infection. Anticapsular and anti-MSCRAMM antibod ies facilitate opsonization in vitro and have been protective against infection in several animal models; however, vaccines with these com ponents have not yet successfully prevented staphylococcal infections in clinical trials. Pathogenesis of Toxin-Mediated Disease S. aureus produces three types of toxins: cytotoxins, pyrogenic toxin superantigens, and exfoliative toxins. Both epidemiologic data and studies in animals suggest that antitoxin antibodies are protective against illness in TSS, staphylococcal food poisoning, and staphylococcal scalded-skin

syndrome (SSSS). Illness develops after toxin synthesis and absorption and the subsequent toxin-initiated host response. ENTEROTOXIN AND TOXIC SHOCK SYNDROME TOXIN 1 (TSST-1) The pyrogenic toxin superantigens are a family of small-molecular-size, structurally similar proteins that are responsible for two diseases: TSS and food poisoning. TSS results from the ability of TSST-1 and enterotoxins to function as T-cell mitogens. In the normal process of antigen presentation, the antigen is first processed within the cell, and peptides are then presented in the major histocompatibility complex (MHC) class II groove, initiating a measured T-cell response. In con trast, TSST-1 and enterotoxins bind directly to the invariant region of MHC—outside the MHC class II groove. TSST-1 and the enterotoxins can then bind T-cell receptors via the vβ chain; this binding results in a dramatic overexpansion of T-cell clones (up to 20% of the total T-cell population). The consequence of this T-cell expansion is a cyto kine storm, with the release of inflammatory mediators that include interferon γ, IL-1, IL-6, TNF-α, and TNF-β. The resulting multisystem disease produces a constellation of findings that mimic those found in endotoxin shock; however, the pathogenic mechanisms differ. A different region of the enterotoxin molecule is responsible for the symptoms of food poisoning. The enterotoxins are heat stable and can survive conditions that kill the bacteria. Illness results from the ingestion of preformed toxin; as a result, the incubation period is short (1–6 h). The toxin stimulates the vagus nerve and the vomiting center of the brain. It also appears to stimulate intestinal peristaltic activity. EXFOLIATIVE TOXINS AND SSSS The exfoliative toxins are responsible for SSSS, most commonly seen in newborns. The toxins that produce disease in humans are of two serotypes: ETA and ETB. These toxins are serine proteases that cleave desmosomal cadherins in the superfi cial layer of the skin, triggering exfoliation. The result is a split in the epidermis at the granular level, which is responsible for the superficial desquamation of

the skin that typifies this illness. ■ ■DIAGNOSIS Staphylococcal infections are readily diagnosed by Gram's stain (Fig. 152-1) and microscopic examination of abscess contents or of infected tissue. Routine cultures of infected material usually are positive; blood cultures are sometimes positive even when infections are localized to extravascular sites. S. aureus is rarely a blood culture contaminant. Polymerase chain reaction (PCR)–based assays are now often used for the rapid diagnosis of S. aureus infection. A number of point-of-care tests are available to screen patients for colonization with MRSA. Determining whether patients with documented S. aureus bacteremia also have infective endocarditis or a metastatic focus of infection remains a diagnostic challenge. Uniformly positive cultures of blood collected over time suggest an endovascular infection such as endocarditis (see "Bacteremia, Sepsis, and Infective Endocarditis," below). ■ ■CLINICAL SYNDROMES (Table 152-1) Skin and Soft Tissue Infections S. aureus causes a variety of cutaneous infections. Common factors predisposing to S. aureus cuta neous infection include chronic skin conditions (e.g., eczema), skin damage (e.g., insect bites, minor trauma), injections (e.g., in diabetes, injection drug use), and poor personal hygiene. These infections are characterized by the formation of pus-containing blisters, which often begin in hair follicles and spread to adjoining tissues. Folliculitis is a superficial infection that involves the hair follicle, with a central area of purulence (pus) surrounded by induration and erythema. Furuncles (boils) are more extensive, painful lesions that tend to occur in hairy, moist regions of the body and extend from the hair follicle to become a true abscess with an area of central purulence. Carbuncles are most often located in the lower neck and are even more severe and painful, resulting from the coalescence of other lesions that extend to a deeper layer of the subcutaneous tissue. In general, furuncles and carbuncles are readily apparent, with pus often expressible or discharging from the abscess. Other cutaneous S. aureus infections include impetigo

TABLE 152-1 Common Illnesses Caused by Staphylococcus aureus Skin and Soft Tissue Infections Folliculitis Abscess, furuncle, carbuncle Cellulitis Impetigo Mastitis Surgical wound infections Musculoskeletal Infections Septic arthritis Osteomyelitis (hematogenous or contiguous spread) Pyomyositis Psoas abscess Respiratory Tract Infections Ventilator-associated or nosocomial pneumonia Septic pulmonary emboli Postviral pneumonia (e.g., influenza) Empyema Bacteremia and Its Complications Sepsis, septic shock Metastatic foci of infection (kidney, joints, bone, lung) Infective endocarditis Infective Endocarditis Injection drug use–associated Native-valve Prosthetic-valve Nosocomial Device-Related Infections (e.g., intravascular catheters, prosthetic joints) Toxin-Mediated Illnesses Toxic shock syndrome Food poisoning Staphylococcal scalded-skin syndrome Invasive Infections Associated with Community-Acquired MethicillinResistant S. aureus Necrotizing fasciitis Waterhouse-Friderichsen syndrome Necrotizing pneumonia Purpura fulminans and cellulitis. S. aureus is one of the most common causes of surgical wound infections. Mastitis develops in 1–3% of nursing mothers. This infection of the breast, which generally presents within 2–3 weeks after delivery, is characterized by findings that range from cellulitis to abscess forma tion. Systemic signs, such as fever and chills, are often present in more severe cases. Musculoskeletal Infections S. aureus is a common cause of bone infections—both those resulting from hematogenous dissemination and those arising from contiguous spread from a soft tissue site. Hema togenous osteomyelitis in children most often involves the long bones. Infections present with fever and bone pain or with a child's reluctance to bear weight. The white blood cell count and erythrocyte sedimen tation rate are often elevated. Blood cultures are positive in ~50% of cases. When necessary, bone biopsies for culture and histopathologic examination are usually diagnostic. In adults, hematogenous osteomyelitis involving the long bones is less common. However,

vertebral osteomyelitis is among the more com mon clinical presentations. Vertebral bone infections are most often

seen in patients with endocarditis, those undergoing hemodialysis, diabetics, and injection drug users. These infections may present with intense back pain and fever but may also be clinically occult, present ing as chronic back pain with low-grade fever. S. aureus is the most common cause of epidural abscess, a complication that can result in neurologic compromise. Patients report difficulty voiding or walking and radicular pain in addition to the symptoms associated with their osteomyelitis. Surgical intervention in this setting often constitutes a medical emergency.

Magnetic resonance imaging (MRI) is the most reliable imaging modality to help establish the diagnosis of osteomyelitis (Fig. 152-3). Routine x-rays are an appropriate first step, but findings may be normal for up to 14 days after the onset of symptoms. If an MRI is not possible, computed tomography (CT) is an acceptable alternative. Bone infections that result from contiguous spread tend to develop from soft tissue infections, such as those associated with diabetic or vascular ulcers, surgery, or trauma. Exposure of bone, a draining fistulous tract, failure to heal, or continued drainage suggests involve ment of underlying bone. Bone involvement is established by bone culture and histopathologic examination (revealing evidence of PMN infiltration). Contamination of culture material from adjacent tissue can make the diagnosis of osteomyelitis difficult in the absence of pathologic confirmation. Samples obtained during surgery are the most reliable. An MRI is the most reliable radiologic test to distinguish between osteomyelitis and overlying soft tissue infection with underly ing osteitis. In both children and adults, S. aureus is the most common cause of septic arthritis in native joints. If left untreated, this infection is rapidly progressive and may be associated with extensive joint destruction. It presents with intense pain on motion of the affected joint, swelling, and fever. Aspiration of the joint reveals turbid fluid, with >50,000 PMNs/μL and gram-positive cocci in clusters seen on Gram’s stain (Fig. 152-1). In adults, septic arthritis may result from trauma, surgery, or hematogenous dissemination. The most commonly involved joints include the knees, shoulders, hips, and phalanges. Infection frequently develops in joints previously damaged by osteoarthritis or rheumatoid CHAPTER 152 Staphylococcal Infections FIGURE 152-3 S. aureus vertebral osteomyelitis and epidural abscess involving the thoracic disk between T9 and T10. Sagittal postcontrast magnetic resonance imaging of the spine illustrates destruction of the T9–T10 intervertebral space with enhancement (long arrow). There is impingement on the thoracic cord and an epidural collection extending from T9 through T11 (short arrows).

arthritis. Iatrogenic infections resulting from aspiration or injection of agents into the joint also occur. In these settings, the patient experi ences increased pain and swelling in the involved joint in association with fever.

Pyomyositis is an unusual infection of skeletal muscles that is seen primarily in tropical climates but also occurs in immunocompromised (e.g., HIV-infected) patients. It is believed to arise from occult bacte remia. Pyomyositis presents as fever, swelling, and pain overlying the involved muscle. Aspiration of fluid from the involved tissue yields pus. Although a history of trauma may be associated with the infection, its pathogenesis is poorly understood. Respiratory Tract Infections Respiratory tract infections caused by S. aureus occur in selected clinical settings. S. aureus is a cause of serious respiratory tract infections in newborns and infants; these infections present with shortness of breath, fever, and respiratory failure. Chest x-ray may reveal pneumatoceles (shaggy,

thin-walled cavities). Pneumothorax and empyema are recognized complications. In adults, nosocomial S. aureus pulmonary infections are common among intubated patients in intensive care units. Nasally colonized patients are at increased risk of these infections. The clinical presenta tion is no different from pulmonary infections caused by other bacterial pathogens. Patients produce increased volumes of purulent sputum and develop respiratory distress, fever, and new pulmonary infiltrates. Dis tinguishing bacterial pneumonia from respiratory failure or other causes of new pulmonary infiltrates in critically ill patients is difficult and relies on a constellation of clinical, radiologic, and laboratory findings. Community-acquired respiratory tract infections due to S. aureus often follow viral infections—most commonly influenza. Patients may present with fever, bloody sputum production, and midlung-field pneumatoceles or multiple, patchy pulmonary infiltrates. Diagnosis is made by sputum Gram's stain and culture. Blood cultures, although useful, are usually negative. Bacteremia, Sepsis, and Infective Endocarditis S. aureus bacteremia may be complicated by sepsis, endocarditis, vasculitis, or metastatic seeding (establishment of suppurative collections at other tissue sites). Among the more commonly seeded tissue sites are bones, joints, kidneys, and lungs. The frequency of metastatic seeding during bacteremia has been estimated to be as high as 31%. The incidence of these complications increases with the duration of the bacteremia. PART 5 Infectious Diseases Recognition of these complications by clinical criteria alone is chal lenging. Comorbid conditions that are frequently seen in association with S. aureus bacteremia and that increase the risk of complications include diabetes, HIV infection, and renal insufficiency. Other host factors that increase the risk of complications include presentation with community-acquired S. aureus bacteremia, lack of an identifiable primary focus of infection, and the presence of prosthetic devices or material. Clinically, S. aureus sepsis presents in a manner similar to that docu mented for sepsis due to other bacteria. The well-described progres sion of hemodynamic changes—beginning with respiratory alkalosis and clinical findings of hypotension and fever—is commonly seen. The microbiologic diagnosis is established by positive blood cultures. The overall incidence of S. aureus endocarditis has increased over the past 20 years. S. aureus is now the leading cause of endocarditis worldwide, accounting for 25–35% of cases. This increase is due, at least in part, to the increased use of intravascular devices and, more recently, the upsurge in injection drug use. Studies using transesopha geal echocardiography found an endocarditis incidence of ~25% among patients with intravascular catheter–associated S. aureus bacte remia. Other factors associated with an increased risk of endocarditis are hemodialysis, the presence of intravascular prosthetic devices at the time of bacteremia, and immunosuppression. Patients with implant able cardiac devices (e.g., permanent pacemakers) are at increased risk of endocarditis or device-related infections. Despite the availability of effective antibiotics, mortality rates from these infections continue to range from 20 to 40%, depending on both the host and the nature of the infection. Complications of S. aureus endocarditis include cardiac valvular insufficiency, peripheral emboli, metastatic seeding, vasculitis,

and central nervous system (CNS) involvement (e.g., mycotic aneu rysms, embolic strokes). S. aureus endocarditis is encountered in four clinical settings: (1) right-sided endocarditis in association with injection drug use; (2) leftsided native-valve endocarditis; (3) prosthetic-valve endocarditis; and (4) nosocomial endocarditis. In each of these settings, the diagnosis is suspected from the patient's history and the recognition of physical signs suggestive of endocarditis. These findings include cardiac mani festations, such as new or changing cardiac valvular murmurs; cuta neous evidence, such as vasculitic lesions, Osler's nodes, or Janeway lesions; evidence of right- or left-sided embolic disease; and a history suggesting a risk for S. aureus bacteremia. In the absence

of anteced ent antibiotic therapy, blood cultures are almost uniformly positive. Transthoracic echocardiography, while less sensitive than transesopha geal echocardiography, is less invasive and often identifies valvular vegetations. The Duke criteria (Chap. 133) are commonly used to help establish this diagnosis. Acute right-sided tricuspid valvular S. aureus endocarditis is most often seen in patients who inject drugs. The classic presentation includes a high fever, a toxic clinical appearance, pleuritic chest pain, and the production of purulent, sometimes bloody, sputum. Chest x-rays or CT scans reveal evidence of septic pulmonary emboli (small, peripheral, circular lesions that may cavitate with time) (Fig. 152-4). A high percentage of affected patients have no history of antecedent val vular damage. At the outset of their illness, patients may present with fever alone, without cardiac or other localizing findings. As a result, a high index of clinical suspicion is essential for diagnosis. Individuals with antecedent cardiac valvular damage more com monly present with left-sided native-valve endocarditis involving the damaged valve. These patients tend to be older than those with rightsided endocarditis, their prognosis is worse, and their incidence of complications (including peripheral emboli, cardiac decompensation, cerebrovascular events, and metastatic seeding) is increased. S. aureus is one of the more common causes of prosthetic-valve endocarditis. This infection is especially fulminant in the early post operative period and is associated with increased morbidity and mor tality. In most instances, medical therapy alone is not sufficient and urgent valve replacement is necessary. Patients are prone to develop valvular insufficiency or myocardial abscesses originating from the region of valve implantation. The increased frequency of nosocomial endocarditis (15–30% of cases, depending on the series) reflects in part the increased use of intravascular devices. This form of endocarditis is most commonly caused by S. aureus. These patients are often critically ill, are receiving antibiotics for various other indications, and have comorbid condi tions. As a result, blood cultures may be negative, and the diagnosis missed. Prosthetic Device–Related Infections S. aureus accounts for a large proportion of prosthetic device–related infections. These infections include intravascular and peritoneal catheters, prosthetic valves, orthopedic devices, pacemakers, left ventricular assist devices, or vascular grafts. In contrast with the more indolent presentation of FIGURE 152-4 Computed tomography scan illustrating septic pulmonary emboli in a patient with methicillin-resistant Staphylococcus aureus bacteremia.

NSaS infections, S. aureus device-related infections are often acute, have both local and systemic manifestations, and tend to progress more rapidly. It is relatively common for a pyogenic collection to be present at the device site. Aspiration of these collections and performance of blood cultures are important components in establishing a diag nosis. S. aureus infections tend to occur more commonly soon after implantation unless the device is used for access (e.g., intravascular or hemodialysis catheters). In the latter instance, infections can occur at any time. As in most prosthetic-device infections, successful therapy usually involves removal of the device. Left in place, the device serves as a potential nidus for either persistent or recurrent infections. Urinary Tract Infections Urinary tract infections (UTIs) are infrequently caused by S. aureus. The presence of S. aureus in the urine often suggests hematogenous dissemination. Ascending S. aureus infections occasionally result from instrumentation of the genitouri nary tract. Infections Associated with Community-Acquired MRSA Although skin and soft tissues are by far the most common sites of infection associated with CA-MRSA, 5–10% of these infections are invasive and can be life-threatening. The latter unique infections, including necrotizing fasciitis, necrotizing pneumonia, and sepsis with Waterhouse-Friderichsen syndrome or purpura fulminans, were rarely associated with S. aureus prior to the emergence of CA-MRSA. These life-threatening infections reflect the

increased virulence of CA-MRSA strains. Toxin-Mediated Diseases • FOOD POISONING S. aureus is among the most common causes of foodborne outbreaks in the United States. Staphylococcal food poisoning results from the inoculation of toxin-producing S. aureus into food by colonized food handlers. Toxin is then elaborated in such growth-promoting food as custards, potato salad, or processed meats. Even if the bacteria are killed by warming, the heat-stable toxin is not destroyed. The onset of illness is rapid, occurring within 1–6 h of ingestion; it is characterized by nausea and vomiting, although diarrhea, hypotension, and dehydration may occur. The differential diagnosis includes diarrhea of other etiologies, especially that caused by similar toxins (e.g., the toxins elaborated by Bacillus cereus). The rapidity of onset, the absence of fever, and the epidemic nature of the presentation (without secondary spread) should arouse suspicion of staphylococcal food poisoning. Symptoms gener ally resolve within 8–10 h. The diagnosis can be established by the demonstration of bacteria or the documentation of enterotoxin in the implicated food. Treatment is entirely supportive. TOXIC SHOCK SYNDROME TSS gained attention in the early 1980s, when a nationwide outbreak occurred among young, otherwise healthy, menstruating women. Epidemiologic investigation demonstrated that these cases were associated with the use of a highly absorbent tampon recently introduced to the market. Subsequent studies established the role of TSST-1 in these illnesses. Withdrawal of the tampon from the market resulted in a rapid decline in the incidence of this disease. However, menstrual and nonmenstrual cases continue to be reported. Nonmenstrual cases are seen in patients with surgical or postpartum wound infections, especially when packing of the wound occurs. The clinical presentation is similar in menstrual and nonmenstrual TSS. Evidence of clinical S. aureus infection is not a prerequisite. TSS results from the elaboration of an enterotoxin or the structurally related enterotoxin-like TSST-1. More than 90% of menstrual cases are caused by TSST-1, whereas a high percentage of nonmenstrual cases are caused by enterotoxins (e.g., enterotoxin B). TSS begins with relatively nonspecific flulike symptoms. In menstrual cases, the onset usually comes 2 or 3 days after the start of menstruation. Patients present with fever, hypotension, and erythroderma of variable inten sity. Mucosal involvement is common (e.g., conjunctival hyperemia). The illness can rapidly progress to symptoms that include vomiting, diarrhea, confusion, myalgias, and abdominal pain. These symptoms reflect the multisystemic nature of the disease, with involvement of the liver, kidneys, gastrointestinal tract, and/or CNS. Desquamation of the skin occurs during convalescence, usually 1–2 weeks after the onset of

TABLE 152-2 Case Definition of Staphylococcus aureus Toxic Shock Syndrome Clinical Criteria An illness with the following clinical manifestations: • Fever: temperature ≥102.0°F (≥38.9°C) • Rash: diffuse macular erythroderma • Desquamation: 1–2 weeks after rash onset • Hypotension: systolic blood pressure ≤90 mmHg for adults or less than the fifth percentile, by age, for children <16 years old • Multisystem involvement (≥3 of the following organ systems) • Gastrointestinal: vomiting or diarrhea at illness onset • Muscular: severe myalgia or creatine phosphokinase level at least twice ULN • Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia • Renal: blood urea nitrogen or creatinine level at least twice ULN for laboratory or urinary sediment with pyuria (≥5 leukocytes per high-power field) in the absence of urinary tract infection • Hepatic: total bilirubin or aminotransferase level at least twice ULN for laboratory • Hematologic: platelet count <105/μL • Central nervous system: disorientation or alterations in consciousness without focal neurologic signs in the absence of fever and hypotension Laboratory Criteria Negative results in the following tests, if obtained: • Blood or cerebrospinal fluid cultures for another pathogena • Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles CHAPTER 152 Case

Classification Probable: a case that meets the laboratory criteria and in which four of the five clinical criteria are fulfilled Confirmed: a case that meets the laboratory criteria and in which all five of the clinical criteria are fulfilled, including desquamation (unless the patient dies before desquamation occurs) Staphylococcal Infections aBlood cultures may be positive for S. aureus. Abbreviation: ULN, upper limit of normal. Source: Centers for Disease Control and Prevention (www.cdc.gov/nndss/ conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/). illness. Laboratory findings may include azotemia, leukocytosis, hypo albuminemia, thrombocytopenia, and liver function abnormalities. Diagnosis of TSS still depends on a constellation of findings rather than one specific finding and on a lack of evidence of other possible infections (Table 152-2). These other diagnoses include drug toxicities, viral exanthems, Rocky Mountain spotted fever, sepsis, and Kawasaki disease. Illness occurs only in persons who lack antibody to TSST-1. Recurrences are possible if antibody fails to develop after the illness. STAPHYLOCOCCAL SCALDED-SKIN SYNDROME SSSS primarily affects newborns and children. The illness may vary from a localized blister to exfoliation of much of the skin surface. The skin is usually fragile and often tender, with thin-walled, fluid-filled bullae (Fig. 152-5). Gentle pressure results in rupture of the lesions, leaving denuded underlying skin. The mucous membranes are usually spared. In more generalized infection, there are often constitutional symptoms, including fever, lethargy, and irritability with poor feeding. Significant amounts of fluid can be lost in more extensive cases. Illness usually follows localized infection at one of several possible sites. SSSS is much less common among adults but can follow infections caused by exfoliative toxin– producing strains. NON–S. AUREUS STAPHYLOCOCCAL INFECTIONS Although less virulent than S. aureus, NSaS are among the most com mon causes of prosthetic-device infections, including endocarditis. They also are increasingly a cause of native-valve endocarditis and life-threatening bloodstream infections in neonates and in neutropenic patients. Approximately half of the identified NSaS species have been associated with human infections. Of these species, Staphylococcus

FIGURE 152-5 Staphylococcal scalded skin syndrome in a 6-year-old boy. Nikolsky’s sign, with separation of the superficial layer of the outer epidermal layer, is visible. (Adapted from LA Schenfeld: Staphylococcal scalded skin syndrome: N Engl J Med 342:1178, 2000.) epidermidis is the most common human pathogen. It is part of the normal human flora and is found on the skin (where it is the most abundant bacterial species) as well as in the oropharynx and vagina. Staphylococcus saprophyticus, a novobiocin-resistant species, is a com mon pathogen in UTIs. ■ ■PATHOGENESIS S. epidermidis is the NSaS species most often associated with pros thetic-device infections. Infection is a two-step process, with initial adhesion to the device followed by colonization. S. epidermidis is uniquely adapted to colonize these devices because of its capacity to elaborate the extracellular polysaccharide (glycocalyx or slime) that facilitates formation of a protective biofilm on the device surface. PART 5 Infectious Diseases Implanted prosthetic material is rapidly coated with host matrix molecules such as fibrinogen or fibronectin. These molecules serve as potential bridging ligands, facilitating initial bacterial attachment to the device surface. A number of staphylococcal surface-associated proteins, such as autolysin (AtlE), fibrinogen-binding protein, and accumulation-associated protein (AAP), appear to play a role in attach ment to either modified or unmodified prosthetic surfaces. The poly saccharide intercellular adhesin facilitates subsequent staphylococcal colonization, aggregation, and accumulation on the device surface. Intercellular adhesin (ica) genes are more commonly found in strains of S. epidermidis that are associated with device infections than in strains associated with colonization of mucosal surfaces. Biofilm acts as a barrier, protecting bacteria from host defense mechanisms as well as from

antibiotics while providing a suitable environment for bacterial maturation, survival, and potential spread to other tissue sites. Two additional NSaS species, Staphylococcus lugdunensis and Staph ylococcus schleiferi, produce more serious infections (native-valve endocarditis and osteomyelitis) than do other NSaS. The basis for this enhanced virulence is not known, although both species appear to share more virulence determinants with S. aureus (e.g., clumping factor and lipase) than do other NSaS. The capacity of S. saprophyticus to cause UTIs in young women appears related to the presence of adhesins that facilitate adherence to uroepithelial cells. A 160-kDa hemagglutinin/adhesin may contribute to this affinity. ■ ■DIAGNOSIS Although the detection of NSaS at sites of infection or in the blood stream by standard microbiologic culture methods is not difficult, interpretation of these results is frequently problematic. Because these organisms are present in large numbers on the skin, they often con taminate cultures. It has been estimated that only 10–20% of blood cul tures positive for NSaS reflect true bacteremia. Similar problems arise with cultures obtained from other sites. Among the clinical findings

suggestive of true bacteremia are fever, evidence of local infection (e.g., erythema or purulent drainage at the IV catheter site), leukocytosis, and systemic signs of sepsis. Laboratory findings suggestive of true bacteremia include repeated isolation of the same strain (i.e., the same species with the same antibiogram or with a closely related DNA fin gerprint) from separate cultures, growth of the strain within 48 h, and bacterial growth in both aerobic and anaerobic bottles. ■ ■CLINICAL SYNDROMES NSaS cause a variety of prosthetic device–related infections, including those that involve prosthetic cardiac valves and joints, vascular grafts, intravascular devices, and CNS shunts. In all of these settings, the clinical presentation is similar. The signs of localized infection are often subtle, the rate of disease progression is slow, and the systemic findings are often limited. Signs of infection, such as purulent drainage, pain at the site, or loosening of prosthetic implants, are sometimes evident. Fever is frequently but not always present, and there may be mild leu kocytosis. Acute-phase reactant levels, erythrocyte sedimentation rate, and C-reactive protein concentration may be elevated. Infections that are not associated with prosthetic devices include, as noted, native-valve endocarditis due to NSaS, which accounts for ~5% of cases. Infections in preterm infants and neutropenic patients are often associated with the need for intravascular devices. S. lugdunensis

appears to be a more aggressive pathogen in this setting, causing greater mortality and rapid valvular destruction with abscess formation than other NSaS. TREATMENT Staphylococcal Infections GENERAL PRINCIPLES OF THERAPY Source control (e.g., incision and drainage of suppurative collec tions or removal of infected prosthetic devices), coupled with rapid institution of appropriate antimicrobial therapy, is essential for the management of all staphylococcal infections. The emergence of MRSA as a community-based pathogen has increased the impor tance of culturing all sites of infection to determine antimicrobial susceptibility and optimize oral treatment regimens. DURATION OF ANTIMICROBIAL THERAPY Therapy for S. aureus bacteremia is generally prolonged (4–6 weeks) because of the high risk of complications (e.g., endocarditis, meta static foci of infection). Among the findings associated with com plicated bacteremias are (1) persistently positive blood cultures 96 h after institution of therapy, (2) failure to promptly remove or drain an identified focus of infection (i.e., an intravascular cathe ter), (3) the presence of deep-seated infections, and (4) acquisition of the infection in the community. Patients with uncomplicated bacteremias are defined by a removable focus of infection, prompt response to antimicrobial therapy (i.e., no fever or positive blood cultures after 3–4 days), no evidence of metastatic foci of

infection, and no implanted prostheses. In these latter infections, shortcourse therapy (2 weeks) can be given; however, these findings are not always predictive of an uncomplicated bacteremia. Given these concerns, caution is therefore needed in instituting a short course of therapy. Transesophageal echocardiography to rule out endocarditis is generally necessary because neither clinical nor laboratory findings can reliably detect cardiac involvement. A thorough radiologic investigation to identify potential metastatic collections is also indicated. All symptomatic body sites must be carefully evaluated. Recent studies have demonstrated that parenteral therapy is not always necessary to complete a course of treatment for invasive staphylococcal infections such as endocarditis or osteomyelitis for carefully selected patients. These include patients with uncompli cated staphylococcal bacteremia. NSaS treatment is complicated by the possibility that a single iso late may be a contaminant. Therapy for 7–14 days is recommended

for documented infections (i.e., blood cultures of the same strain ≥24 h apart) in the absence of endocarditis or additional sites of infection. CHOICE OF ANTIMICROBIAL AGENTS The choice of antimicrobial agents to treat both coagulase-positive and coagulase-negative staphylococcal infections is often difficult because of the prevalence of multidrug-resistant strains and the limited number of clinical trials that have compared the available TABLE 152-3 Antimicrobial Therapy for Staphylococcal Infectionsa SENSITIVITY/ RESISTANCE OF ISOLATE DRUG OF CHOICE ALTERNATIVE(S) COMMENTS Parenteral Therapy for Serious Infections Sensitive to penicillin Penicillin G (4 mU q4h) Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8hb) Sensitive to methicillin; resistant to penicillin Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h) Daptomycin (6–10 mg/kg IV q24hb,d), vancomycin (15–20 mg/kg q8hb), ceftobiprole (500 mg IV q6hg) Resistant to methicillin Vancomycin (15–20 mg/kg

q8–12hb), daptomycin (6–10 mg/kg IV q24hb,d) for bacteremia, endocarditis, osteomyelitis, and complicated skin infections Linezolid (600 mg q12h PO or IV), ceftaroline (600 mg IV q8–12h), telavancin (7.5–10 mg/kg IV q24h)b, TMP-SMX (5 mg [based on TMP]/kg IV q8–12h)f Additional agents include tedizolid (200 mg once daily IV), oritavancin (single dose of 1200 mg), dalbavancin (single dose of 1500 mg), delafloxacin (300 mg q 12 h IV), omadacycline 100 mg OD). Ceftobiprole (500 mg IV q6hg) Resistant to methicillin with intermediate or complete resistance to vancomycine Daptomycin (6–10 mg/kg q24hb,d) for bacteremia, endocarditis, osteomyelitis, and complicated skin infections Same as for methicillin-resistant strains (check antibiotic susceptibilities) or Ceftaroline (600 mg IV q8–12h) Newer agents include tedizolid (200 mg once daily IV or PO), oritavancin (single dose of 1200 mg), and dalbavancin (single dose of 1500 mg). These drugs are approved only for the treatment of skin and soft tissue infections. Not yet known (i.e., empirical therapy) Vancomycin (15–20 mg/kg q8–12hb), daptomycin

(6–10 mg/kg q24hb,d) for bacteremia, endocarditis, osteomyelitis, and complicated skin infections — Empirical therapy is given when the susceptibility of the isolate is not known. Vancomycin with or without a b-lactam is recommended for suspected community- or hospital-acquired Staphylococcus aureus infections because of the increased frequency of methicillin-resistant strains in the community. If isolates with an elevated MIC to vancomycin (≥1.5 μg/mL) are common in the community, daptomycin may be preferable. Oral Therapy for Skin and Soft Tissue Infections Sensitive to methicillin Dicloxacillin (500 mg qid), cephalexin (500 mg qid), or cefadroxil (1 g q12h) Minocycline or doxycycline (100 mg q12hb), TMPSMX (1 or 2 DS tablets bid), clindamycin (300–450 mg tid), linezolid (600 mg PO q12h), tedizolid

(200 mg PO q24h) Resistant to methicillin Clindamycin (300–450 mg tid), TMP-SMX (1 or 2 DS tablets bid), minocycline or doxycycline (100 mg q12hb), linezolid (600 mg bid), or tedizolid (200 mg once daily) Delafloxacin 450 mg q12 h, omadacycline 300 mg once a day aRecommended dosages are for adults with normal renal and hepatic function. bThe dosage must be adjusted for patients with reduced creatinine clearance. cFor the treatment of prosthetic-valve endocarditis, the addition of gentamicin (1 mg/kg q8h) and rifampin (300 mg PO q8h) is recommended, with adjustment of the gentamicin dosage if the creatinine clearance rate is reduced. dDaptomycin cannot be used for the treatment of pneumonia. eVancomycin-resistant S. aureus isolates from clinical infections have been reported. fTMP-SMX may be less effective than vancomycin. gAdditional studies are needed. Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate S. aureus; VRSA, vancomycin-resistant S. aureus. Source: Modified from C Liu et al: Clin Infect Dis 52:285, 2011; DL Stevens et al: Clin Infect Dis 59:148, 2014; DL Stevens et al: Med Lett Drugs Ther 56:39, 2014; and LM Baddour et al: Circulation 132:1435, 2015.

agents. Staphylococcal resistance to most antibiotic families, includ ing β-lactams, aminoglycosides, fluoroquinolones, and (to a lesser extent) glycopeptides, has increased. This trend is even more appar ent with NSaS; >80% of nosocomial isolates are resistant to methi cillin, and these methicillin-resistant strains are often resistant to other antibiotics. Because the selection of antimicrobial agents for S. aureus infections is similar to that for NSaS infections, treatment options for these pathogens are discussed together and are sum marized in Table 152-3.

Fewer than 5% of isolates are sensitive to penicillin. The clinical microbiology laboratory must verify that the strain is not a b-lactamase producer. Patients with a penicillin allergy can be treated with a cephalosporin if the allergy does not involve an anaphylactic or accelerated reaction; desensitization to b-lactams may be indicated in selected cases of serious infection when maximal bactericidal activity is needed (e.g., prostheticvalve endocarditisc). Vancomycin is a less effective option than a b -lactam. Sensitivity testing is necessary before an alternative drug is selected. The efficacy of adjunctive therapy is not well established in many settings. Linezolid, ceftaroline, and telavancin have in vitro activity against most VISA and VRSA strains. See footnote for treatment of prostheticvalve endocarditis.c CHAPTER 152 Staphylococcal Infections Same as for methicillin-resistant strains; check antibiotic susceptibilities. Ceftaroline is used either alone or in combination with daptomycin. It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All collections should be drained, and drainage should be cultured. It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All collections should be drained, and drainage should be cultured.

Few strains of staphylococci (≤5%) remain susceptible to peni cillin. This is a result of the widespread dissemination of plasmids containing the enzyme penicillinase. Penicillin-resistant isolates are treated with semisynthetic penicillinase-resistant penicillins (SPRPs), such as oxacillin or nafcillin. Methicillin, the first of the SPRPs, is no longer used. Cephalosporins are alternative therapeutic agents for these infections. In patients with a history of serious β-lactam allergies, alternatives to SPRPs for the treatment of invasive infec tions should be used only after careful consideration. Desensitiza tion to β-lactams remains an option for life-threatening infections. Second- and third-generation cephalosporins offer no therapeutic advantage over first-generation cephalosporins for the treatment of staphylococcal infections, and some third-generation

cephalosporins (e.g., ceftazidime, ceftriaxone) have considerably less activity and should be avoided. The carbapenems have excellent activity against methicillin-sensitive S. aureus but not against MRSA.

The isolation of MRSA was reported within 1 year of the intro duction of methicillin. Since then, the prevalence of MRSA has steadily increased. In many U.S. hospitals and elsewhere, 40–50% of S. aureus isolates are resistant to methicillin. Resistance to methicil lin indicates resistance to all SPRPs as well as to all cephalosporins (except ceftaroline). Production of a novel penicillin-binding pro tein (PBP2a) is responsible for methicillin resistance. This protein is synthesized by the mecA gene, which (as stated above) is part of a large mobile genetic element—a pathogenicity or genomic island—called SCCmec. It is hypothesized that mecA was acquired via horizontal transfer from related staphylococcal species. Phe notypic expression of methicillin resistance may be constitutive (i.e., expressed in all cells in a population) or heterogeneous (i.e., displayed by only a proportion of the total cell population). Detec tion of methicillin resistance is enhanced by growth of cultures at reduced temperatures (≤35°C for 24 h) and with increased concen trations of salt in the medium. Culture techniques are increasingly being replaced by PCR-based or other methods (e.g., latex aggluti nation) that allow for the rapid detection of methicillin resistance. PART 5 Infectious Diseases Either vancomycin or daptomycin is recommended as the drug of choice for the treatment of invasive MRSA infections. MRSA susceptibility to vancomycin has decreased in many areas of the world. It is important to note that vancomycin is less effective than SPRPs for the treatment of infections due to methicillin-susceptible strains. Three types of staphylococcal resistance to vancomycin have emerged. (1) Minimal inhibitory concentration (MIC; an in vitro measure of susceptibility) “creep” refers to the incremental increase in vancomycin MICs that has been detected in various geographic areas. Studies suggest that morbidity and mortality may be increased in infections due to S. aureus strains with vancomycin MICs of ≥1.5 μg/mL. (2) In 1997, an S. aureus strain with reduced suscepti bility to vancomycin (vancomycin-intermediate S. aureus [VISA]) was reported from Japan. Subsequently, additional VISA clinical isolates were reported. These strains were resistant to methicillin and many other antimicrobial agents. The VISA strains appear to evolve (under vancomycin selective pressure) from strains that are susceptible to vancomycin but are heterogeneous, with a small proportion of the bacterial population expressing the resistance phenotype. The mechanism of VISA resistance is in part due to an abnormally thick cell wall. Vancomycin is trapped by the abnormal peptidoglycan cross-linking and is unable to gain access to its target site. Regulatory genes involved in cell wall metabolism appear to play an important role in this type of resistance. (3) In 2002, the first clinical isolate of fully vancomycin-resistant S. aureus (VRSA) was reported. Resistance in this and several additional clinical isolates was due to the presence of vanA, the gene responsible for expression of vancomycin resistance in enterococci. This observa tion suggested that resistance was acquired as a result of horizontal conjugal transfer from a vancomycin-resistant strain of Enterococcus faecalis. Several of the patients infected with the VRSA strain had both MRSA and vancomycin-resistant enterococci cultured from infection sites. The vanA gene is responsible for the synthesis of

the dipeptide d-Ala-d-Lac in place of d-Ala-d-Ala. Vancomycin cannot bind to the altered peptide. While isolates with MICs of ≥1.5 μg/mL have been relatively common in some areas, VISA and VRSA isolates are uncommon. Daptomycin, a parenteral bactericidal agent with antistaphylo coccal activity, is approved for the treatment of bacteremia (includ ing right-sided endocarditis) and complicated skin infections. It is not effective in respiratory infections. This drug has a unique

mechanism of action: it disrupts the cytoplasmic membrane. Staph ylococcal resistance to daptomycin has been reported. Resistance can emerge during therapy; patients previously treated with van comycin may have elevated daptomycin MICs. Patients need to be monitored for rhabdomyolysis with creatine phosphokinase mea surement and for eosinophilic pneumonia. Linezolid—the first oxazolidinone—is bacteriostatic against staphylococci; it offers the advantage of comparable bioavailability after oral or parenteral administration. Cross-resistance with other inhibitors of protein synthesis has not been detected. Resistance to linezolid is rare but has been reported. Serious adverse reactions to linezolid include thrombocytopenia, occasional cases of neutro penia, and rare instances of lactic acidosis or peripheral and optic neuropathy. These reactions tend to occur after relatively prolonged courses of therapy. Tedizolid, a second oxazolidinone, is available as both oral and parenteral preparations. It exhibits enhanced in vitro activity against antibiotic-resistant gram-positive bacteria, including staph ylococci. Tedizolid is administered once a day. Data on its efficacy for the treatment of deep-seated infections are limited. Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA (including strains with reduced susceptibil ity to vancomycin and daptomycin). It is generally well tolerated. Ceftaroline is approved for use in nosocomial pneumonias and for SSTIs. It has increasingly been used to treat invasive MRSA infec tions with or without glycopeptides. Telavancin is a parenteral lipoglycopeptide derivative of van comycin that is approved for the treatment of complicated SSTIs and for nosocomial pneumonias. The drug has two targets: the cell wall and the cell membrane. It remains active against VISA strains. Because of its potential nephrotoxicity, telavancin should be avoided in patients with renal disease. Dalbavancin and oritavancin are long-acting, parenterally administered lipoglycopeptides that have been used to treat com plicated SSTIs. Because of their long half-lives, they can be admin istered on a weekly basis. Both have been used as single-dose regimens for the treatment of SSTIs. Emerging data support their use for the treatment of invasive staphylococcal infections. Although the quinolones are active against staphylococci in vitro, the frequency of staphylococcal resistance to these agents has increased, especially among methicillin-resistant isolates. Of particular concern in MRSA is the possibility of quinolone resis tance emerging during therapy. Therefore, quinolones are not recommended for the treatment of MRSA infections. Resistance to the quinolones is most commonly chromosomal and results from mutations of the topoisomerase IV or DNA gyrase genes, although multidrug efflux pumps also may contribute. Although the newer quinolones exhibit increased in vitro activity against staphylococci, it is uncertain whether this increase translates into enhanced in vivo activity. Delafloxacin, a fluoroquinolone with broad-spectrum activity, has excellent activity against MRSA, retaining activity against some isolates resistant to other fluoroquinolones. Tigecycline, a broad-spectrum minocycline analogue, has bac teriostatic activity against MRSA and is approved for use in SSTIs as well as intraabdominal infections caused by S. aureus. It is not recommended for the treatment of invasive infections. Other older antibiotics, such as minocycline, doxycycline, clindamycin, and trimethoprim-sulfamethoxazole, continue to be successfully used to treat MRSA infections. Ceftobiprole is a new antibiotic with excellent activity against both MRSA and methicillin-susceptible S. aureus (MSSA). It has

been shown in clinical trials to be effective in treating complicated staphylococcal bacteremias, SSTIs, and pneumonia. The benefit of antistaphylococcal combinations to enhance bactericidal activity in the treatment of deep-seated infections remains controversial. Clinical studies have not documented a therapeutic benefit from the addition of gentamicin to single-drug regimens; recent reports have raised concern about the potential nephrotoxicity of gentamicin and adverse

reactions from, or drug interactions with, rifampin. As a result, the use of gentamicin in combination with β-lactams or other antimicrobial agents is no longer routinely recommended for the treatment of invasive infec tions such as native-valve endocarditis. Rifampin continues to be used for the treatment of prosthetic device–related infections and for osteomyelitis. Omadacycline and eravacycline are broad-spectrum semisyn thetic tetracycline derivatives with activity against MRSA. They are currently approved for the treatment of SSTIs. The use of bacteriophages with activity against staphylococci is now being investigated in clinical trials as adjunctive therapy in invasive infections. ANTIMICROBIAL THERAPY FOR SELECTED SETTINGS Empirical Therapy Empirical coverage for MRSA is indicated when antibiotic susceptibility is not known. Vancomycin or daptomycin is generally recommended. It remains uncertain whether daptomycin is preferable when elevated vancomycin MICs (>1.5 μg/mL) are com mon in a specific locale. Salvage Therapy Salvage therapy for complicated S. aureus infec tions is sometimes needed when the bacteremia persists (i.e., for 3 days) despite appropriate treatment. The risk of a poor outcome (i.e., increased mortality, metastatic infections) is increased with the duration of bacteremia. Prolonged bacteremia can occur with both MRSA and MSSA. There is limited high-quality evidence to serve as a guide to salvage therapy. The combination of daptomycin or vancomycin with a β-lactam antibiotic (e.g., ceftaroline) has been successfully used to treat patients with persistent MRSA bactere mia, even those patients with isolates displaying reduced suscep tibility to these antimicrobial agents. This combination appears to enhance the bactericidal activity of daptomycin by reducing the bacterial cell-surface charge and thus allowing enhanced dapto mycin binding. For vancomycin, the combination may allow more strategic binding to the target site with reduced cell-wall thickness. Other combinations have included trimethoprim-sulfamethoxazole or rifampin combined with daptomycin. Linezolid and ceftaroline have also been used as single alternative agents. Endocarditis S. aureus endocarditis is usually an acute, lifethreatening infection. Thus, prompt collection of blood for cul tures should be followed by immediate institution of empirical antimicrobial therapy. For native-valve endocarditis, therapy with a β-lactam is recommended. If a MRSA strain is isolated, vancomycin (15–20 mg/kg every 8–12 h, given in equal doses up to a total of 2 g, with the dose adjusted in the case of renal disease) or daptomycin (6–10 mg/kg every 24 h) is recommended. The vancomycin dose should be adjusted based on area under the curve (AUC)-based dosing, although measurement of trough levels may also be used. Patients are generally treated for 6 weeks. For prosthetic-valve endocarditis, surgery in addition to antibiotic therapy is often nec essary. The combination of a β-lactam agent—or, if the isolate is β-lactam-resistant, vancomycin or daptomycin—with an aminogly coside (gentamicin, 1 mg/kg IV every 8 h) for 2 weeks and rifampin (300 mg orally or IV every 8 h) for ≥6 weeks is recommended. Infectious diseases and, if necessary, surgical consultation should be considered. Bone and Joint Infections For hematogenous osteomyelitis or septic arthritis in children, a 4-week course of therapy is usually adequate. In adults, treatment is often more prolonged. For chronic forms of osteomyelitis, surgical debridement is necessary in com bination with antimicrobial therapy. For joint infections, a critical

component of therapy is the repeated aspiration or arthroscopy of the affected joint to prevent damage from leukocytes. The combi nation of rifampin with ciprofloxacin has been used successfully to treat or suppress prosthetic-joint infections, especially when the device cannot be removed. The efficacy of this combination may reflect enhanced activity against staphylococci in biofilms as well as the attainment of effective intracellular concentrations.

Skin and Soft Tissue Infections The increase in SSTIs caused by CA-MRSA has drawn attention to the need for initiation of appropriate empirical therapy. Even small abscesses appear to ben efit from antibiotic therapy in addition to incision and drainage. Antibiotics are selected depending on local antibiotic susceptibility data; several oral agents have been used to treat these infections, including clindamycin, trimethoprim-sulfamethoxazole, doxycy cline, linezolid, and tedizolid. Parenteral therapy is reserved for more complicated infections. Toxic Shock Syndrome Treatment of shock is the mainstay of therapy for TSS. Both fluids and pressors may be necessary. Tam pons or other packing material should be promptly removed. Some investigators recommend therapy with a combination of clindamy cin and a semisynthetic penicillin or (if the isolate is resistant to methicillin) vancomycin. Clindamycin is advocated because, as a protein synthesis inhibitor, it reduces toxin production. Linezolid also appears to be effective. A semisynthetic penicillin or a glyco peptide is recommended to eliminate any potential focus of infec tion as well as to eradicate persistent carriage that might increase the possibility of recurrence. Intravenous immunoglobulin to treat TSS is of uncertain benefit. Glucocorticoids are not recommended for the treatment of this disease. CHAPTER 152 Other Toxin-Mediated Diseases Therapy for staphylococcal food poisoning is entirely supportive. For SSSS, antistaphylococcal therapy targets the primary site of infection. NONTRADITIONAL APPROACHES TO ANTISTAPHYLOCOCCAL THERAPY In addition to the development of new antibiotics, new and non traditional approaches to therapy are currently being investigated. These include the use of phages or phage-derived peptides, as well as probiotics and antivirulence strategies that target selected viru lence determinants. Staphylococcal Infections ■ ■PREVENTION Primary prevention of S. aureus infections in the hospital setting involves hand washing and careful attention to appropriate isolation procedures. Through careful screening for MRSA carriage and strict isolation practices, several Scandinavian countries have been remark ably successful at preventing the introduction and dissemination of MRSA in hospitals. Decolonization strategies, using both universal and targeted approaches with topical agents (e.g., mupirocin) to eliminate nasal colonization and/or chlorhexidine to eliminate colonization of addi tional body sites with S. aureus, have been successful in some clinical settings where the risk of infection is high (e.g., intensive care units). An analysis of clinical trials suggests that decolonization can reduce the incidence of postsurgical infections among people nasally colonized with S. aureus. The risk of recurrent admissions among patients with

S. aureus bacteremia following discharge is high (~22% within 30 days). Decolonization following discharge with mupirocin and chlorhexidine can lower the incidence of recurrent infections. “Bundling” (the application of selected medical interventions in a sequence of prescribed steps) has reduced rates of nosocomial infec tions related to procedures such as the insertion of intravenous cath eters, in which staphylococci are among the most common pathogens (see Table 147-1). A number of immunization strategies to prevent S. aureus infections—both active (e.g., capsular polysaccharide–protein conjugate vaccine) and passive (e.g., clumping factor antibody)—have been investigated. However, to date, none has been successful for either prophylaxis or therapy in clinical trials.

Revision #1
Created 2026-01-06 16:33:02 UTC by Omar Ayman
Updated 2026-01-06 16:33:03 UTC by Omar Ayman