Staphylococcus Infections in the ICU
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Objectives
- Appreciate the scope and importance of Staphylococcus infections in critically ill patients
- Understand the principles behind appropriate diagnosis and effective management
- Discuss points of pharmacotherapy that are relevant for the daily practice of critical care

Key words: Staphylococcus aureus, methicillin resistance, sepsis, shock, bacteremia, infective endocarditis

Staphylococcus aureus is a unique microorganism in that it is both a commensal organism and a virulent human pathogen. Some 30% to 50% of healthy adults are colonized with S. aureus, of whom 10% to 20% are persistently colonized. Persons colonized with S. aureus are at increased risk for subsequent invasive infections.1 The mortality rate of S. aureus bacteremia was about 82% in the preantibiotic era and seems to have plateaued at 15% to 50% over the past several decades.2,3 S. aureus remains one of the most commonly encountered pathogens in the critically ill population. About 30% of sepsis cases in the ICU are due to S. aureus, and half of these isolates are methicillin resistant.4 Despite the overall predominance of gram-negative infections in ICUs, S. aureus is 1 of the 2 most commonly isolated pathogens.5

The proposed stages in the pathogenesis of S. aureus infections are colonization, local infection, systemic dissemination (sepsis), metastatic infection, and toxinosis.1 Specific factors allow the organism to hinder natural host defenses and promote the spread of disease. These include structural proteins, toxins, and enzymatic factors. Structural proteins, for example, protein A, assist in colonization of hosts and in mechanisms to avert opsonization and phagocytosis. Cytotoxins, such as α-toxin, play a role in pore formation and cellular damage, which may contribute to the pathogenesis of sepsis. The pyrogenic-toxin superantigens include toxic shock syndrome toxin 1 (TSST-1) and most of the staphylococcal enterotoxins, which function by binding to major histocompatibility complex (MHC) class II proteins, causing extensive T-cell proliferation and cytokine release. Panton-Valentine leukocidin (PVL) is a leukocytolytic toxin that has been epidemiologically associated with severe cutaneous infections and necrotizing pneumonia. Various enzymes, such as protease, lipase, and hyaluronidase, facilitate the spread of infection to adjoining tissues.1

Life-threatening staphylococcal infections may be the cause (eg, severe cellulitis, necrotizing pneumonia, infective endocarditis) or consequence (eg, central line–associated bloodstream infection, surgical site infection, ventilator-associated pneumonia) of critical illness. Increasing healthcare exposure, expansion of an aging population, increased numbers of immunocompromised hosts, and increasing use of invasive medical devices have led to an increase in staphylococcal infections. S. aureus remains unparalleled in the variety and severity of illness that it can produce. Table 1 provides an outline of the different staphylococcal infections that could be encountered in a critical care setting. The purpose of this chapter is to outline the various aspects of staphylococcal infections that are relevant to the daily practice of critical care. This chapter focuses on S. aureus infections and will only briefly mention coagulase-negative Staphylococcus species (CoNS). Drug resistance mechanisms and other detailed aspects of pharmacology also are not discussed.

S. aureus Bacteremia and Infective Endocarditis

Epidemiological Characteristics

S. aureus is the leading cause of bacteremia and infective endocarditis.6 In 2009, the rate of S. aureus bacteremia in the United States was found to be close to 38.2 episodes per 100,000 person-years in certain populations,7 whereas in 2013, the annual international incidence was
about 26.1 per 100,000 population. While the overall incidence of *S. aureus* bacteremia is stable, methicillin-resistant *S. aureus* (MRSA) bacteremia is on the rise. S. aureus bacteremia is usually complicated, up to half of patients will develop metastatic infections, up to a fourth may develop endocarditis, and the 12-week mortality rate is about 20% to 24%. Thus, *S. aureus* identified in blood culture should never be regarded as a “contaminant.” The *S. aureus* bacteremia (SAB) scoring system was devised to evaluate a patient’s risk of complicated bacteremia. This scoring assigns 1 point each for community-acquired infection, skin findings suggestive of acute systemic infection, and persistent fever at 72 hours. The system assigns 2 points for a positive result of follow-up blood culture at 48 to 96 hours. The predicted rate of complications is 16% if no risk factors are present, and it increases with the presence of each risk factor to a predicted rate of 90% if all risk factors are present. Certain patient populations, including those with primary *S. aureus* bloodstream infections, patients receiving hemodialysis, intravenous drug users, people with diabetes, and those with preexisting cardiac conditions, are at higher risk of developing complications from *S. aureus* bacteremia.

### Table 1. Spectrum of Disease Caused by *Staphylococcus aureus*

<table>
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<th>Organ System</th>
<th>Disease Conditions</th>
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| General/multisystem        | Septic shock  
Toxic shock syndrome  
Purpura fulminans   |
| Circulatory/cardiovascular | Bloodstream infections (community- or healthcare-acquired)  
Infective endocarditis (native or prosthetic valve)   |
| Pleuropulmonary            | Community-acquired pneumonia  
Hospital-acquired pneumonia  
Ventilator-associated pneumonia  
Lung abscess  
Septic pulmonary emboli  
Necrotizing pneumonia  
Empyema   |
| Skin/muscular              | Cellulitis  
Necrotizing fascitis  
Surgical site infections  
Pyomyositis  
Scalded skin syndrome  
Botryomycosis   |
| Central nervous system     | Meningitis  
Ventriculitis  
Brain abscess  
Septic emboli  
Spinal epidural abscess   |
| Osteoarticular             | Acute and chronic osteomyelitis  
Septic arthritis  
Prosthetic joint infections  
Septic bursitis   |
| Gastrointestinal           | Food-borne gastroenteritis   |
| Visceral infections        | Renal abscess  
Pyogenic hepatic abscess  
Splenic abscess   |
including infective endocarditis. Endovascular, lower respiratory tract, abdominal, and central nervous system (CNS) foci of \textit{S} \textit{aureus} infections are viewed as high-risk sources for mortality compared with other sources. Source control and removal of infected lines and foreign objects are crucial in the management of \textit{S} \textit{aureus} bacteremia, and failure to do so is associated with increased mortality. Infective endocarditis has an estimated annual incidence of 3 to 9 cases per 100,000 in industrialized countries, with an in-hospital mortality rate up to 22% and a 5-year mortality rate of 40% in industrialized countries. \textit{S} \textit{aureus} not only is the leading cause of infective endocarditis in industrialized nations but also is an independent predictor of mortality in this condition.

**Complicated Versus Uncomplicated \textit{S} \textit{aureus} Bacteremia**

Uncomplicated bacteremia was characterized by Fowler et al as a case that fulfills all of the following criteria: catheter-associated infection and removal of the catheter, negative result of follow-up blood cultures, defervescence within 72 hours, normal findings on transesophageal echocardiogram, no prosthetic material in the joints or intravascular space, and no symptoms suggestive of metastatic infection. A 2-week treatment duration from the first negative blood culture is required to treat uncomplicated \textit{S} \textit{aureus} bacteremia. All others would qualify as complicated \textit{S} \textit{aureus} bacteremia cases and require 4 to 6 weeks of therapy.

**Role of Echocardiography**

All patients with \textit{S} \textit{aureus} bacteremia should undergo echocardiography to assist in stratifying their bacteremia as complicated or uncomplicated. Detection of infective endocarditis is higher with transesophageal echocardiography (about 14%-28%) than with transthoracic echocardiography (about 2%-15%). Factors associated with low risk of infective endocarditis include absence of a permanent intracardiac device, sterile follow-up blood cultures within 4 days after the initial set, no hemodialysis dependence, nosocomial acquisition of \textit{S} \textit{aureus} bacteremia, absence of secondary foci of infection, and lack of clinical signs of infective endocarditis. Transesophageal echocardiography is preferred for most patients with \textit{S} \textit{aureus} bacteremia. Transthoracic echocardiography may be adequate only for patients without identified risk factors for infective endocarditis.

**Medical Management of \textit{S} \textit{aureus} Bacteremia and Infective Endocarditis**

Failure to remove foreign devices, patient dependence on hemodialysis, and the use of vancomycin for methicillin-sensitive \textit{S} \textit{aureus} (MSSA) bacteremia are risk factors for relapse of \textit{S} \textit{aureus} bacteremia and treatment failure. Antistaphylococcal \(\beta\)-lactam agents are the drugs of choice to manage MSSA bacteremia. Choices include the antistaphylococcal penicillins (ASPs) or first-generation cephalosporins, such as cefazolin. Daptomycin also may be used for MSSA bacteremia and right-sided endocarditis. Vancomycin and daptomycin are currently the only antibiotics that are approved by the US Food and Drug Administration (FDA) for MRSA bacteremia and right-sided infective endocarditis. Infectious diseases consultation is associated with increased adherence to standards of care, such as using \(\beta\)-lactam antibiotics for MSSA bacteremia, providing longer durations of therapy for complicated \textit{S} \textit{aureus} bacteremia, removing infected catheters and devices, obtaining follow-up blood cultures and echocardiography, and draining abscesses.

For uncomplicated, right-sided, native valve endocarditis secondary to MSSA, 2 weeks of either ASPs, cefazolin, or daptomycin or 4 weeks of vancomycin is recommended. The addition of gentamicin for MSSA bacteremia and native valve endocarditis is no longer recommended due to lack of clinical benefit and increased nephrotoxicity. Recommended treatments for uncomplicated, left-sided, native valve endocarditis are 6 weeks of ASP or cefazolin for MSSA and 6 weeks of vancomycin or daptomycin (\(\geq\)8 mg/kg) for MRSA. In patients with MSSA left-sided endocarditis with septic emboli to the brain, cefazolin should be avoided due to lack of sufficient CNS penetration of first-generation cephalosporins. Recommended treatments for prosthetic valve
endocarditis are 6 weeks or more of ASP or ceftazolin plus rifampin for MSSA and 6 weeks or more of vancomycin plus rifampin for MRSA, each with 2 weeks of gentamicin. These infections can manifest as pulse-generator pocket infection or bloodstream infection with or without endocarditis. Reported mortality rates of cardiac device–related endocarditis range from 31% to 66% if the infected device is not removed. Mortality rate of 18% is reported with combined medical treatment and complete device removal. Obtaining blood cultures in all cases is recommended. If blood cultures are positive or if prior antibiotics were used (which could confound blood culture results), a transesophageal echocardiogram is recommended. For infections of the pocket site only without positive blood cultures, complete device removal with 10 to 14 days of targeted antibiotic therapy is recommended. When blood cultures are positive and transesophageal echocardiogram shows lead vegetation without complications (ie, without osteomyelitis, septic thrombosis, endocarditis), complete device removal and 2 to 4 weeks of targeted antibiotics are recommended. If complications including endocarditis or metastatic infections are present with lead vegetation, then 4 to 6 weeks of targeted antimicrobial therapy is warranted with complete device removal. Device removal is crucial to ensure full clearance of infection but may not be risk-free or possible in every case. Device removal should be planned based on the risk and benefit in each individual patient. After device removal, reininsertion should be carefully reconsidered because up to one-third of patients may no longer need their device. Generally, the new device should be placed after 14 days from the first negative blood cultures in patients with CIED-related endocarditis, after 72 hours from the first negative blood cultures in those with lead vegetation or bloodstream infection without endocarditis, and after resolution of local signs of infection in those who had a pocket site infection only. The replacement should be implanted on the contralateral side of the removed device. Long-term antimicrobial suppressive therapy is used in selected patients with CIED infections who are not candidates for device removal.

**Key Points**
- The clinician should determine whether *S aureus* bacteremia is complicated or uncomplicated.
- Echocardiogram and evaluation for metastatic infection should be performed in all cases.
- The patient should receive targeted antimicrobial therapy of appropriate duration.
- Infectious diseases experts should be consulted in cases of *S aureus* bacteremia.
- The clinician should ensure source control and removal of foreign bodies.
- Vancomycin should be avoided for MSSA infections.
- Cefazolin should be avoided for MSSA infections when CNS involvement is suspected.

**Infections of Cardiovascular Implantable Electronic Devices**

The use of cardiovascular implantable electronic devices (CIEDs), including permanent pacemakers and implantable cardioverter-defibrillators, has increased substantially. The reported incidence of cardiac device infection is higher for implantable cardioverter-defibrillators than for permanent pacemakers. *Staphylococcus* species account for 60% to 80% of CIED infections, with the majority of cases caused by CoNS and *S aureus*. These infections can manifest as pulse-generator pocket infection or bloodstream infection with or without endocarditis. Reported mortality rates of cardiac device–related endocarditis range from 31% to 66% if the infected device is not removed. Mortality rate of 18% is reported with combined medical treatment and complete device removal. Obtaining blood cultures in all cases is recommended. If blood cultures are positive or if prior antibiotics were used (which could confound blood culture results), a transesophageal echocardiogram is recommended. For infections of the pocket site only without positive blood cultures, complete device removal with 10 to 14 days of targeted antibiotic therapy is recommended. When blood cultures are positive and transesophageal echocardiogram shows lead vegetation without complications (ie, without osteomyelitis, septic thrombosis, endocarditis), complete device removal and 2 to 4 weeks of targeted antibiotics are recommended. If complications including endocarditis or metastatic infections are present with lead vegetation, then 4 to 6 weeks of targeted antimicrobial therapy is warranted with complete device removal. Device removal is crucial to ensure full clearance of infection but may not be risk-free or possible in every case. Device removal should be planned based on the risk and benefit in each individual patient. After device removal, reininsertion should be carefully reconsidered because up to one-third of patients may no longer need their device. Generally, the new device should be placed after 14 days from the first negative blood cultures in patients with CIED-related endocarditis, after 72 hours from the first negative blood cultures in those with lead vegetation or bloodstream infection without endocarditis, and after resolution of local signs of infection in those who had a pocket site infection only. The replacement should be implanted on the contralateral side of the removed device. Long-term antimicrobial suppressive therapy is used in selected patients with CIED infections who are not candidates for device removal.

**Infections With Use of Extracorporeal Membrane Oxygenation and Left Ventricular Assist Devices**

The overall prevalence of infection in adults receiving extracorporeal membrane oxygenation (ECMO) is about 20.9%. CoNS and *S aureus*
are 2 of the most common organisms that cause infections in this population. Bloodstream infections are the most common source of infection, followed by surgical site infection, urinary infection, and respiratory tract infection. No evidence is available to show that the routine use of prophylactic antibiotics reduces the risk of infection. Staphylococcus epidermidis and S aureus together are responsible for 57% of all infections related to the use of a left ventricular assist device (LVAD). Persistent local trauma and poor healing at the driveline exit site may provide a site of local infection from which invasive disease may develop. LVAD-associated bloodstream infection may be indistinguishable from LVAD-related endocarditis. These infections frequently delay transplantation and lead to increased posttransplant hospital stay and increased short-term mortality after transplant. Management often requires continuous antibiotic therapy for weeks and is complicated by drug toxicity and potential colonization or infection with drug-resistant organisms (particularly vancomycin-resistant Enterococcus faecium). As opposed to continuous treatment from the time of diagnosis of LVAD-related infections through the posttransplant period, limited treatment increases the risk for relapse and LVAD superinfection. These are highly complicated cases that require multispecialty management, which should include local expert opinion from surgical specialists, critical care providers, and infectious disease specialists.

**Key Points**

- Device removal is crucial for complete cure in CIED infections.
- Transesophageal echocardiography should be performed when blood cultures are positive or prior antibiotics were used.
- Treatment should continue from diagnosis to the posttransplant period for LVAD-associated infections.
- Antimicrobial prophylaxis does not reduce the rate of infections during ECMO.

**Pleuropulmonary Infections**

S aureus is capable of producing a full spectrum of pulmonary illness, including community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), necrotizing pneumonia, empyema, septic pulmonary emboli, and lung abscess. MSSA and MRSA account for 1.6% and 0.7% of cases of CAP, respectively, yet empirical coverage for MRSA in CAP was noted to be almost 30%. In the absence of certain risk factors or disease characteristics, empirical coverage for MRSA does not seem justified in CAP. Among community-acquired infections, a certain subset of importance is community-acquired MRSA (CA-MRSA), containing staphylococcal cassette chromosome mec (SCCmec) type IV as well as the gene encoding PVL. Pneumonia in young, previously healthy adults with a preceding influenza-like illness characterized by severe respiratory symptoms, hemoptysis, high fever, leukopenia, hypotension, and a chest radiograph showing multilobular, cavitary alveolar infiltrates should lead one to suspect CA-MRSA infection. These are extremely sick patients; 80% of them are admitted to ICU, 62% require endotracheal intubation, 46% require chest tube placement, and one-third of them die from this disease. Hemoptysis, erythroderma, and leukopenia have been associated with lower survival. Treatment is generally supportive, with admission to the ICU, drainage of empyema (if present), and a combination of parenteral antibiotic treatment. Clindamycin and linezolid markedly suppress the formation of PVL, α-hemolysin, and TSST-1. Intravenous immunoglobulin (IVIG) has been shown to neutralize the damaging pore-forming effect of PVL on polymorphonuclear neutrophils and may be considered in severe cases, but robust clinical data are lacking and no uniform recommendations are available. No consensus on treatment duration is available, but 7 to 21 days of therapy (generally ≥14 days) has been observed depending on disease severity and clinical response.
**S aureus** is the most commonly isolated bacterial pathogen in HAP and VAP, being associated with almost 30% of cases. For VAP alone, 20% to 30% of cases are caused by *S aureus* (approximately half of these are due to MRSA); about 16% of HAP cases are due to *S aureus* (10% are due to MRSA). Inadequate and/or delayed treatment is associated with higher mortality rates. A gold standard for the microbiological diagnosis of HAP or VAP has not been established, but noninvasive sampling with nonquantitative cultures is generally favored in the current guidelines. The negative predictive value of sputum Gram stain for diagnosing VAP is 91%, suggesting that VAP is unlikely with a negative Gram stain (in a patient with low pretest probability of VAP). The positive predictive value of Gram stain, however, is only about 40%, and it correlates poorly with organisms identified in the final culture. A positive Gram stain should not be used to narrow anti-infective therapy until the final culture results become available. Recent or concurrent antibiotic therapy will obviously alter these results and should be considered during the interpretation of Gram stain and culture results.

Empirical treatment for MRSA should be provided to patients with certain risk factors, including intravenous antibiotic therapy in the past 90 days, septic shock, acute respiratory distress syndrome prior to VAP, acute renal replacement therapy prior to VAP, hospitalization for 5 days prior to VAP, known prior colonization with MRSA, need for ventilator support due to HAP, and septic shock in the setting of HAP. Additionally, in units where greater than 10% of *S aureus* isolates are methicillin-resistant and in units where the prevalence of MRSA is not known, treatment should include empirical MRSA coverage. Either vancomycin or linezolid may be used for the therapy of HAP or VAP due to MRSA. No conclusive evidence is available to show that either of these agents is superior to the other. Linezolid was found to have higher clinical cure rates without any survival benefit over vancomycin; however, more patients receiving vancomycin required mechanical ventilation, and vancomycin levels were suboptimal in more than half of these patients. Given the comparable outcomes for vancomycin and linezolid in randomized clinical trials, the decision for either agent should be based on individual patient factors such as blood cell counts, renal function, concurrent nephrotoxic therapy, potential drug interactions, and cost. None of the other agents (including teicoplanin, telavancin, tedizolid, and ceftaroline) have been found to be as effective as either vancomycin or linezolid in the treatment of MRSA pneumonia. Daptomycin is inhibited by pulmonary surfactant and should not be used in the treatment of pneumonia. For patients without any of the noted risk factors for MRSA, empirical antibiotics should include coverage for MSSA. Antibiotic combinations including piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem generally provide adequate empirical coverage for MSSA, but once final cultures are available, definitive therapy should be completed with oxacillin, nafcillin, or cefazolin for proven MSSA. Vancomycin treatment for MSSA pneumonia has been associated with mortality rates close to 50%, whereas antistaphylococcal β-lactams have been associated with 5% mortality. Deescalation of antibiotics is recommended using a combination of clinical information and procalcitonin levels. A short course of therapy (7 days on average) for HAP and VAP is now recommended irrespective of microbial cause. Exceptions include patients with empyema, lung abscess, evidence of extrapulmonary origin, or spread of infection including secondary bacteremia (bacteremic pneumonia), which are frequent indications for longer therapy. *S aureus* is known to cause about one-third of cases of empyema. Empyema develops in 10% to 24% of patients who have *S aureus* pneumonia. Empyema complicating trauma, surgery, or hemothorax is commonly caused by *S aureus*. Management of these patients should be similar to that for patients with other causes of empyema, with longer courses of antibiotics frequently coupled with pleural drainage and/or local fibrinolytic therapy and surgery.
Key Points

- Coverage for MRSA in patients with CAP is generally unnecessary.
- Providers must recognize clinical features of necrotizing CA-MRSA pneumonia.
- Coverage with vancomycin or linezolid should be provided for suspected VAP and HAP.
- Gram stain has a high negative predictive value in low-risk patients.
- Daptomycin should not be used to treat pneumonia.
- Treating MSSA pneumonia with vancomycin leads to high mortality.

Central Nervous System Infections

Spinal Epidural Abscess

Although rare overall, spinal epidural abscess has doubled in prevalence in the past 2 decades due to increases in spinal instrumentation, increases in intravenous drug use, and improvements in radiological diagnostic modalities.30 *S. aureus* is the most common causative agent, accounting for 60% to 73% of all cases.3 An epidural abscess may arise by hematogenous seeding from an episode of *S. aureus* bacteremia, by contiguous spread from an adjacent focus (such as psoas abscess or vertebral osteomyelitis), or by direct inoculation from trauma, spinal surgery, or the placement of epidural catheters. Approximately 2.5% of patients with *S. aureus* bacteremia may have epidural abscesses. Four stages of clinical presentation are known: stage 1, back pain at the affected vertebral level; stage 2, nerve root pain radiating from the involved area; stage 3, objective motor and sensory loss and/or bladder and bowel dysfunction; and stage 4, paralysis. Epidural abscesses are a medical and surgical emergency and must be urgently evaluated for laminectomy, decompression, and debridement, especially if the patient presents in stage 2 or 3. If paralysis has been present for more than 48 hours, it is more likely to be permanent. Appropriate antistaphylococcal therapy for MSSA or MRSA is required for 6 weeks, with appropriate surgical intervention as indicated.5,30

Meningitis and Ventriculitis

*S. aureus* meningitis has 2 distinct pathogenic mechanisms. In postoperative meningitis, bacteria are introduced during neurosurgical procedures, during placement of a cerebrospinal fluid (CSF) shunt device, localized trauma during surgery, or by spreading from contiguous infection. In hematogenous meningitis, *S. aureus* is disseminated systemically after bacteremic spread from infection outside the CNS.31 Hematogenous *S. aureus* meningitis is usually community acquired and, compared with postsurgical meningitis, typically affects older individuals with severe medical comorbidities such as diabetes or chronic kidney disease. The mortality rate for hematogenous *S. aureus* meningitis is higher (43%-50%) than that for postoperative meningitis (14%-25%).31 Risk factors for postoperative meningitis include the presence of an intrathecal device or ventriculoperitoneal (VP) shunt, recent neurosurgery, or CSF leak. Abnormalities of CSF cell count, glucose, and/or protein may not be reliably present in patients with healthcare-associated ventriculitis and meningitis, and even a negative Gram stain of the CSF may not rule out these infections. An elevated CSF level of lactate or procalcitonin, or the combination of both, may be useful in the diagnosis of healthcare-associated bacterial ventriculitis and meningitis.32 Nucleic acid amplification tests on CSF, such as polymerase chain reaction (PCR), may increase the clinician’s ability to identify a pathogen and decrease the time to make a specific diagnosis.32 High-dose parenteral nafcillin or oxacillin to treat MSSA meningitis and vancomycin for MRSA meningitis are recommended generally for 10 to 14 days. If CSF cultures are repeatedly positive with appropriate therapy, treatment should be continued for 10 to 14 days after the last positive culture.3,32 Intraventricular antimicrobial therapy should be considered for healthcare-associated ventriculitis and meningitis when the infection responds poorly to systemic antimicrobial therapy alone.32 If the isolate is susceptible, rifampin should be added for combination therapy, especially when hardware, such as drains or shunts, is present.
Total removal of infected VP shunts, intrathecal pumps, CSF drains, and deep brain stimulators is required for complete clearance of infection. A new shunt may be reimplanted 10 days after negative CSF cultures.32

Key Points

• Spinal epidural abscess requires a high index of suspicion for diagnosis.

• Spinal epidural abscess is a medical and surgical emergency.

• Treatment for spinal epidural abscess should entail 6 weeks of antibiotics and appropriate surgical care.

• Removal of infected CNS hardware is needed in meningitis and ventriculitis.

• Meningitis and ventriculitis require 10 to 14 days of therapy from the last positive culture.

Staphylococcal Toxic Shock Syndrome

Staphylococcal toxic shock syndrome (STSS) remains a fairly rare but severe disease. Mortality rates are higher for the nonmenstrual form of the disease.3 Currently, half of all cases of STSS are associated with nonmenstrual form of the disease. Colonization with toxigenic strains of S aureus and lack of antibody response to the toxin are prerequisites for disease development and recurrence.33 TSST-1 is the toxin isolated in the majority of cases. This toxin is responsible for more than 90% of STSS cases associated with menstruation and about 50% to 60% of nonmenstrual cases.34 Most of the cases in which TSST-1 is not present are caused by staphylococcal enterotoxin B. These bacterial toxins act as superantigens, activating very large numbers of T cells and generating an overwhelming, immune-mediated cytokine response that creates the clinical picture of shock with multiorgan failure. A confirmed case must meet all of the following diagnostic criteria: (1) temperature higher than 38.9°C (102°F), (2) shock (systolic blood pressure <90 mm Hg despite adequate fluid resuscitation), (3) a diffuse macular erythematous rash (typically followed 1-2 weeks later by desquamation), and (4) specific abnormalities involving at least 3 organ systems. The organ systems that can be involved are (1) gastrointestinal (vomiting or diarrhea); (2) musculoskeletal (severe myalgia or creatinine kinase levels >2 times the upper limit of normal); (3) renal (serum creatinine levels >2 times the upper limit of normal); (4) hepatic (bilirubin or transaminase levels >2 times the upper limit of normal); (5) hematological (platelet counts of <100,000 platelets/μL); and (6) CNS (delirium without focal signs).3 Bacteremia is rarely associated with this disease. Nonmenstrual disease may occur after vaginal and cesarean delivery, respiratory tract infections (including upper respiratory tract infections), soft tissue infection, endovascular infection, visceral abscesses, and use of barrier contraceptives.3,34 Surgical wounds can appear benign at presentation, yet toxin-producing staphylococci can be isolated from samples of such wounds. Primary sites of infection caused by toxin-producing S aureus strains may require aggressive surgical drainage, even in the absence of a well-defined abscess or fluid collection.3 Supportive management, intravenous hydration, hemodynamic support, and, depending on the degree of shock, mechanical ventilation may be required as part of aggressive management. Judicious empirical antibiotic coverage and targeted antibiotics are crucial for successful management. Clindamycin and linezolid have been found to have antitoxin activity. MRSA or MSSA strains should be treated with vancomycin and ASPs, respectively, and ideally should be used in combination with clindamycin. The role of IVIG remains ill-defined, and IVIG generally is not as successful for STSS as it has been for streptococcal disease but has been advocated for severely ill patients.3,34 STSS remains rare and sporadic; therefore, the evidence base for management is limited to case reports and series.

Key Points

• STSS is a clinical diagnosis and requires good supportive care.

• Wounds may need debridement or drainage even in the absence of clinical findings.
• Appropriate anti-staphylococcal antibiotics should be utilized and the addition of clindamycin or linezolid for anti-toxin activity should be considered in severe cases.

• The role of IVIG is uncertain, but it may be tried in severely ill patients.

**Skin and Soft Tissue Infections**

*S. aureus* causes a variety of skin and soft tissue infections (SSTIs), ranging from the benign (eg, impetigo and uncomplicated cellulitis) to the immediately life-threatening (eg, necrotizing fasciitis, severe cellulitis with systemic sepsis). CA-MRSA strains led to increased interest in community cases of severe SSTI. Multiple virulence factors appear to contribute to the ability of CA-MRSA to cause SSTI, including PVL and α-hemolysin (α-toxin). S. aureus is the most common pathogen isolated from surgical site infections (SSIs), cutaneous abscesses, and purulent cellulitis. In the United States, *S. aureus* is less commonly associated with necrotizing fasciitis, but predisposing conditions include intravenous drug use, previous MRSA infections, diabetes mellitus, and hepatitis C infection. All severe nonpurulent skin infections and any significantly purulent skin lesions will require empirical *S. aureus* therapy. Vancomycin, linezolid, daptomycin, telavancin, or ceftaroline may be used for patients hospitalized with a severe purulent SSTI. Patient factors (such as history of drug allergies, renal function, and drug interactions) should determine the choice of drug, and no agent has been found superior to others for this specific indication. For severe and necrotizing infections, empirical therapy should cover MRSA and anaerobes, and recommended combinations include vancomycin plus either piperacillin-tazobactam or a carbapenem. Clindamycin or linezolid may be used for antitoxin activity; no specific recommendations for or against IVIG in staphylococcal disease are available. Aggressive surgical debridement is the mainstay of therapy, with good supportive care and antibiotics as second-line therapy. Surgical Site Infections (SSIs) are the most common adverse event affecting hospitalized surgical patients and account for 38% of nosocomial infections in hospitalized surgical patients. SSIs rarely occur during the first 48 hours after surgery, and fever during that period usually arises from noninfectious causes. SSIs that do occur in this time frame are almost always due to *Streptococcus pyogenes* or *Clostridium* species. A rare cause of early fever and systemic signs following surgery is staphylococcal wound toxic shock syndrome, a condition in which the wound may appear deceptively benign. Fever, hypotension, abnormal hepatic and renal blood studies, and diarrhea are early findings. Appropriate treatment is to open the incision, perform culture, and begin antistaphylococcal treatment immediately. After 48 hours, SSI is a more common source of postoperative fever. The most important therapy for an SSI is to open the incision, evacuate the infected material, and continue dressing changes until the wound heals by secondary intention. Patients with temperature higher than 38.5°C (101.3°F), heart rate higher than 110 beats per minute, or erythema extending beyond the wound margins for more than 5 cm may require a short course of antibiotics (about 24-48 hours), as well as opening of the suture line. SSIs following clean procedures that do not involve the intestinal or genital tract are generally caused by *Streptococcus* or *Staphylococcus* species. High local prevalence of MRSA, prior MRSA infection in the individual patient, MRSA nasal colonization, or previous use of antibiotics should prompt empirical treatment of MRSA with vancomycin, linezolid, daptomycin, telavancin, or ceftaroline. Empirical coverage for *S. aureus* is warranted in all SSIs, and up to 30% of all postoperative infections are caused by this pathogen. In cardiac ICUs, the presence of *S. aureus* bacteremia after sternotomy for cardiac surgery is likely to indicate mediastinitis, which could be a particularly devastating condition. The presence of other pathogens in the blood postoperatively is less likely to be associated with this condition. The duration of therapy for most severe SSTIs is about 7 to 14 days, but an individual approach may be required in
each case depending on patient risk factors and clinical improvement.  

**Key Points**  
- Severe nonpurulent and all purulent skin conditions require treatment for *S aureus*.  
- SSIs are uncommon as the cause of postoperative fever less than 48 hours after surgery.  
- Toxigenic infections including wound STSS can present in the early postoperative period.  
- Poststernotomy *S aureus* bacteremia could indicate mediastinitis.

### Osteoarticular Infections

*S aureus* is the most common pathogen in all 3 major classes of osteoarticular infection: namely, osteomyelitis, native joint septic arthritis, and prosthetic joint infection (PJI).  

#### Osteomyelitis

Osteomyelitis may be caused by 1 of 3 well-recognized mechanisms: (1) local spread from a contiguous contaminated source of infection (eg, after trauma), (2) osteomyelitis related to vascular insufficiency (eg, associated with diabetes), and (3) hematogenous osteomyelitis.  

Hematogenous infections generally involve the ends of long bones in children and adolescents and the axial skeleton in older adults. The ability of *S aureus* to invade cells may explain its capacity to colonize tissues and persist. *S aureus* expresses numerous surface proteins that mediate adherence to components of bone matrix and collagen. Additionally, biofilm formation acts as a barrier against penetration of antimicrobial agents and nutrients. *S aureus* can invade osteoblasts and form small-colony variants in the intracellular compartment, where they are able to survive in a metabolically inactive state while preserving the integrity of the host cell. Given their slow growth and intracellular survival, small-colony variants are difficult to eradicate with standard antibiotic therapy. Osteomyelitis can present with a variety of signs and symptoms, such as an open wound exposing fractured bone, an indolent draining fistula or local swelling, and bone pain with no skin lesion.  

Leukocytosis and elevated erythrocyte sedimentation rate and C-reactive protein are present in the majority of acute hematogenous cases. Diagnostic delays are not uncommon, and a high index of suspicion is required. Magnetic resonance imaging and computed tomography scans are generally used for diagnosis (magnetic resonance imaging being more reliable). Positive blood cultures (present about 60% of the times) in the appropriate clinical context assist in diagnosis. Bone samples for culture and histological assessment should be sought in the absence of positive blood cultures. Administration of antibiotics prior to obtaining bone samples for culture can reduce culture yield by 50%.  

Antibiotics cannot be held if a patient is acutely ill or unstable but should be held when the clinician believes this to be safe. Generally, 6 to 12 weeks of targeted therapy is advised, with most authorities recommending at least 8 weeks of therapy for MRSA. Longer duration of therapy is advised for patients who have a slow clinical response to treatment or a persisting deep focus of infection. For patients responding well to treatment, 2 weeks of parenteral therapy followed by completion of therapy with a suitable oral agent could be recommended. Depending on the site and mechanism of osteomyelitis, surgical debridement plays a major role in management. Chronic osteomyelitis generally requires 1 to 3 months of therapy with or without surgical management.  

#### Septic Arthritis

The knee joint is the most common focus of septic arthritis; hips and shoulders follow, in that order. Septic arthritis is generally monoarticular, but in 10% of cases it can be polyarticular. *S aureus* is the most common cause of septic arthritis. Fever, pain, and swelling over the involved joint are important physical signs. Arthrocentesis is important to make the diagnosis; white blood cell count of synovial fluid between 50,000 and 150,000 cells/mm³ with neutrophilic predominance of more than 90% is suggestive of septic arthritis. Gram stain of the synovial fluid may be revealing in up to 50% of cases, and cultures are positive in majority of individuals who did not receive prior antibiotics.
Crystal arthropathy and hemarthrosis are important differentials of septic arthritis. *S aureus* septic arthritis is associated with poor functional outcome if diagnosis is delayed. Joint debridement and/or drainage and targeted antimicrobial therapy for 3 to 4 weeks are recommended.

**Prosthetic Joint Infections**

With more than 600,000 primary total knee and hip arthroplasty procedures performed in the United States annually, the incidence of PJI is increasing, with up to a 2% annual infection rate. *S aureus* and CoNS account for more than half of cases of prosthetic hip and prosthetic knee infection. Physical findings may not reliably diagnose PJI, and a high index of suspicion is required. Sedimentation rate and C-reactive protein, blood cultures, and a plain radiograph should be obtained to assist in diagnosis. Preoperative arthrocentesis is recommended in all cases, and antibiotics should be withheld in stable patients to improve diagnostic yield. Patients who have a well-fixed prosthesis without a sinus tract who are within 30 days of implantation or less than 3 weeks of onset of infectious symptoms should be considered for debridement and retention of prosthesis. Patients who do not meet these criteria should have prosthetic removal with 1-stage or 2-stage exchange (based on expertise and patient factors). Standard of care for PJI secondary to *S aureus* entails 2 to 6 weeks of a pathogen-specific, intravenous antimicrobial therapy in combination with rifampin twice daily; this is followed by rifampin plus a companion oral drug for a total of 3 months for a total hip arthroplasty infection and 6 months for a total knee arthroplasty infection. Those who are not candidates for prosthetic removal should be maintained on chronic suppressive antimicrobial therapy.

**Key Points**

- A high index of suspicion regarding osteoarticular infection is required.
- If blood cultures are negative, bone samples or joint fluid should be tested.
- Appropriate duration of antibiotics with surgical drainage and/or debridement is required.

**MRSA Prevention in the ICU**

Sixty-five percent of all healthcare-associated infections (HAIs) are reported in the critical care setting. Prevention of *S aureus* and, particularly, MRSA has been of great interest in recent times. Of the various strategies for MRSA prevention, universal decolonization has been found to reduce MRSA infections by 37%, whereas targeted decolonization and screening and isolation may reduce infections by 25% and 8%, respectively. Universal decolonization was also shown to reduce bloodstream infections from any pathogen by 44%. Other potential benefits can include elimination of MRSA surveillance tests and the associated reduction in contact precautions. However, risks must be balanced against these potential benefits. The benefits of decolonization are temporary and might last for up to 90 days, after which recolonization is not uncommon. The impact of chlorhexidine and mupirocin resistance with these strategies is unknown but could be a potential concern, and future surveillance for resistance may be required.

The sensitivities of MRSA screening tests vary considerably by anatomic site and by method of isolation. Although colonization with *S aureus* is a risk factor for invasive infections, antibiotic treatment is ineffective in reducing *S aureus* colonization in the lower airways and preventing invasive pulmonary infections. Only about 30% of respiratory infections are due to MRSA in patients with positive MRSA surveillance studies. In patients with pneumonia, the MRSA PCR nasal swab has a poor positive predictive value but an excellent negative predictive value for MRSA pneumonia in populations with low MRSA pneumonia incidence. In settings with higher prevalence rates of MRSA, a negative screen decreases the probability that infection is due to MRSA but does not rule out the possibility. A low level of evidence and wide variation in clinical practice complicate clinical application. Local infection control policies should be followed.
Molecular Rapid Diagnostic Testing

Every hour of delay in effective therapy after the onset of hypotension in septic shock is associated with an increment in mortality. Compared with an almost 80% survival if appropriate antibiotics are given in the first hour of septic shock, less than half of patients survive septic shock if appropriate therapy is delayed by 5 to 6 hours. Traditional microbiological methods remain suboptimal in providing rapid identification and susceptibility testing, with an average turnaround time estimated to be around 40 hours (and longer in many cases). Inappropriate therapy of MSSA infections with vancomycin and likewise ineffective empirical coverage of MRSA infections with antistaphylococcal β-lactam agents lead to suboptimal outcomes. Rapid diagnostic techniques are now available that have reduced turnaround times to direct focused empirical therapy in bloodstream infections to a couple of hours. Multiplex PCR and hybridization techniques can be applied to positive blood cultures and can rapidly identify *S. aureus* (either as MSSA or MRSA) and CoNS. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) provides rapid results and is capable of analyzing thousands of samples per day from different sources, including blood, respiratory secretions, urine, and wound. A 1- to 2-day reduction in mean time to appropriate therapy may be achieved by using these techniques. This might lead to shorter length of hospital stay and lower mean cost of therapy when used in conjunction with infectious disease pharmacist interventions. Most rewarding is the fact that in combination with antimicrobial stewardship programs (but not without such programs), molecular rapid diagnostic testing has resulted in lower mortality, with 20 such uses needed to prevent 1 death from a gram-positive or gram-negative bloodstream infection. These are compelling reasons to consider using molecular rapid diagnostic testing as standard of care in the diagnosis and management of infections. No randomized trials or robust clinical data exist to support the use of empirical combination therapy with vancomycin plus ASPs or first-generation cephalosporins. Given that the tradeoff is potentially lower mortality, with an opportunity to deescalate therapy based on subsequent data, such empirical combination therapy could be considered for critically ill patients (especially those with septic shock). This combination may especially be considered in facilities where molecular rapid diagnostic testing is not available.

**Key Points**

- Molecular rapid diagnostic testing should be used to reduce time to effective therapy.
- Dual antistaphylococcal coverage may be considered in the sickest of patients where such testing is not available.

**Select Points on Pharmacotherapy**

**Dosing Antibiotics in Critical Illness**

Antimicrobial dosing in critical illness is complex and dynamic. Severe sepsis and septic shock are associated with an increase in renal preload and increased “third spacing” of fluids due to capillary leak, thereby increasing the volume of distribution and clearance of antibiotics. In contrast, multiorgan dysfunction including hepatic and renal impairment might lead to decreased drug clearance. Patients receiving continuous renal replacement therapy require particular attention to ensure appropriate dose adjustments. Optimization of antimicrobial dosing with the assistance of a critical care pharmacist should be considered while treating severe *S. aureus* infections. Pharmacokinetic and pharmacodynamic optimization should be undertaken to improve efficacy and reduce the potential of drug resistance during therapy.

**Antistaphylococcal β-Lactams**

Vancomycin is an inferior choice for MSSA infections. Antistaphylococcal β-lactam agents are the drugs of choice to manage MSSA bacteremia. Choices include the ASPs, such as flucloxacillin (0.25-2 g administered intravenously every 6 hours or by continuous infusion), or first-generation cephalosporins, such as cefazolin (2 g administered intravenously every 8 hours or by continuous infusion), in
patients with normal renal function. The cyclic lipopeptide daptomycin (6 mg/kg administered intravenously once every 24 hours) may also be used for MSSA bacteremia and right-sided endocarditis.\textsuperscript{14,15} Traditiona\textsuperscript{16}ly, ASPs have been favored for select, severe MSSA infections such as infective endocarditis, given concerns of inactivation of cefazolin by type A β-lactamases produced by a large inoculum of \textit{S aureus} (inoculum effect). However, cefazolin has been shown to be equally effective and more economical with fewer side effects and lower discontinuation rates than ASPs.\textsuperscript{47} Deep-seated infections, metastatic infections, and onset of infections while in the ICU, and not necessarily β-lactam agent of choice, are more likely risk factors for treatment failure.\textsuperscript{48} This again highlights the need for adequate source control in addition to antimicrobial therapy to treat \textit{S aureus} infections successfully. More recently, patients treated with cefazolin had a lower risk of mortality with similar odds of recurrent infections compared with patients treated with ASPs for MSSA infections complicated by bacteremia.\textsuperscript{49} However, data on source control, doses used, adverse effects, and postdischarge antibiotics were not available, and these findings may not be generalizable. Cefazolin has limited penetration into the CSF and should not be used for infections involving the CNS.\textsuperscript{49} β-Lactam antibiotics are “time-dependent antibiotics,” and maximal killing rate is achieved at concentrations that are only about 4 times the minimal inhibitory concentration (MIC); antimicrobial killing is optimized by increasing time above MIC for these antibiotics. Prolonged or continuous infusions can therefore optimize the antimicrobial efficacy of β-lactam antibiotics. This may be particularly important in life-threatening infections in critically ill patients as well as in infections with organisms that are more difficult to treat (ie, that have higher MICs). Although no good quality clinical evidence has shown a mortality benefit of continuous infusion of antibiotics to treat \textit{S aureus} infections, continuous infusions have been shown to improve clinical cure rates and increase the number of ventilator-free days and could be considered on an individual basis in the sickest of patients.\textsuperscript{50}

\textbf{Vancomycin}

Vancomycin has been the workhorse for treating MRSA infections for the past 50 years. Vancomycin should not be used for MSSA infections unless there are circumstances that prevent the use of antistaphylococcal β-lactam agents (such as anaphylactic allergic reactions). Vancomycin is not as rapidly bactericidal compared with β-lactam agents. The major current problem associated with increasing vancomycin use over the last several decades is the increasing occurrence of treatment failures due to drug tolerance. Rising MICs to vancomycin appear to be the main mechanism associated with these treatment failures despite these MICs remaining within susceptible range (“MIC creep”). Up to 16.2% of recent \textit{S aureus} isolates tested had a vancomycin MIC of 2 mg/mL.\textsuperscript{51} With pathogens for which the MIC is 2 mg/L or higher, very high daily doses of vancomycin would be required and alternate agents should be used. Vancomycin has a high molecular weight and its penetration into a variety of tissues is limited, which contributes to its limited therapeutic efficacy. The concentration achieved in epithelial lining fluid of the lung in patients undergoing mechanical ventilation is only about 14% of that in serum. Vancomycin also has low concentrations in soft tissue, especially in patients with diabetes.\textsuperscript{51} Despite these drawbacks, vancomycin is still the treatment of choice in MRSA pneumonia and soft tissue infections, and no other agents have been proven superior to vancomycin. Vancomycin should be administered according to body weight (15-20 mg/kg per dose, actual body weight) every 8 to 12 hours, not to exceed 2 g per dose, in patients with normal renal function. In seriously ill patients (eg, those with sepsis, meningitis, pneumonia, or infective endocarditis) with suspected MRSA infection, a loading dose of 25 to 30 mg/kg (actual body weight) should be given. Vancomycin trough concentrations should be monitored and maintained between 15 and 20 μg/mL. Greater
vancomycin trough levels may not necessarily result in improved clinical outcomes. High MIC for vancomycin (MIC ≥1.5 μg/mL by E-test) has been shown to be associated with a worse prognosis in both MRSA and MSSA infections and leads to higher rates of treatment failure and increased mortality rates. Use of alternative agents should be considered when infection with high MIC isolates is suspected or proven. Due to significant changes in vancomycin pharmacokinetics during critical illness, such as increased volume of distribution and augmented clearance, the standard dosing for patients with normal renal function has been associated with inadequate drug concentrations. Continuous infusions of vancomycin are not standard of care currently but may achieve target concentrations more rapidly with a lower daily dose, with more stable drug concentrations and fewer adverse events, than standard intermittent infusion.

**Daptomycin**

Daptomycin is a cyclic lipopeptide that has rapid bactericidal activity against most clinically relevant gram-positive bacteria, including *S. aureus*, by interacting with the plasma membrane and destabilizing its electric potential. This leads to inhibition of protein, DNA, and RNA synthesis and finally bacterial cell death. Daptomycin is approved for the treatment of skin and soft tissue infections at a dose of 4 mg/kg/d and for the treatment of bacteremia and right-sided endocarditis at 6 mg/kg/d, and its bactericidal activity is concentration dependent. Along with vancomycin, daptomycin is the only FDA-approved option for MRSA bacteremia and was shown to be noninferior to standard therapeutic options for both MRSA and MSSA bacteremia. Daptomycin is believed to be an appropriate replacement option for vancomycin as empirical therapy for gram-positive bacteremia, pending culture results. The dosing interval should be adjusted to every 48 hours when the creatinine clearance is less than 30 mL/min. Daptomycin is inactivated by alveolar surfactant and thus should not be used for the treatment of pneumonia. Clinically significant elevations of creatine kinase occur in 6.7% of recipients receiving daptomycin. Patients who are taking daptomycin should be monitored for creatine kinase elevations and skeletal muscle dysfunction. Drug-induced eosinophilic pneumonia has been noted in case reports, and it is treated by stopping the offending agent and administering a course of corticosteroids. A correlation between vancomycin resistance and reduced daptomycin susceptibility has been described; caution should be used in treating these strains with daptomycin. Through novel mechanisms, certain β-lactam agents may restore daptomycin sensitivity, and this combination therapy could be considered for synergy and salvage therapy in carefully selected cases.

**Linezolid**

Linezolid is an oxazolidinone antibiotic that prevents the initiation of protein synthesis by binding the 23S rRNA of the 50S ribosomal subunit. Linezolid is a bacteriostatic agent and is approved for use in skin and soft tissue infections and nosocomial pneumonia secondary to susceptible organisms, including MRSA. Current practice guidelines advise using either linezolid or vancomycin for MRSA pneumonia. A study found evidence that linezolid might lead to better clinical cure rates than vancomycin in MRSA pneumonia, but more patients receiving vancomycin in that study required invasive mechanical ventilation and most did not achieve therapeutic drug levels. Linezolid inhibits the secretion of TSST-1 and other toxins and has been used in necrotizing pneumonia and toxic shock syndrome. Linezolid reaches higher tissue levels in the alveoli and CNS compared with vancomycin. Given its bacteriostatic mechanism of action, linezolid is generally not recommended as first-line therapy in cases of primary bacteremia (unless other therapeutic options are limited). Potential drug interactions are possible with linezolid, particularly the risk of serotonin syndrome when linezolid is used with monoamine oxidase inhibitors or selective serotonin reuptake inhibitors. Fentanyl used in combination with linezolid can increase the risk of serotonin syndrome when a third agent like a monoamine oxidase inhibitor or selective serotonin reuptake inhibitor is also being used. Drug-related side
effects including bone marrow suppression, peripheral and optic neuropathy, and lactic acidosis may develop after 2 or more weeks of therapy.

**Ceftaroline**

Ceftaroline is a cephalosporin with improved affinity against penicillin binding protein 2A, which confers β-lactam resistance in MRSA. Ceftaroline was initially approved for use in skin and soft tissue infections and CAP. Ceftaroline has been shown to be effective in off-label use for bacteremia and osteomyelitis, among other off-label uses. It is a viable treatment option in hospitalized patients with *S. aureus* bacteremia secondary to skin and soft tissue infections and CAP. Combination therapy with daptomycin and ceftaroline was shown to restore daptomycin sensitivity in vivo and resulted in clearance of persistent blood cultures. Trials are ongoing to determine the role of ceftaroline in the management of bacteremia.

**Other Agents**

Tigecycline is effective for skin and soft tissue infections including cases that are resistant to tetracycline. Tigecycline should not be used in cases of bacteremia, as it is bacteriostatic. Tedizolid phosphate is a newer agent that has activity against MRSA and vancomycin-resistant enterococci. Tedizolid maintains activity against linezolid-resistant *S. aureus*. Tedizolid phosphate is available in both oral and intravenous formulations, with once-daily dosing. It may not have clinically significant interactions with serotonergic compounds and might be considered as an alternative to linezolid in patients concomitantly taking serotonergic agents. Tedizolid is being studied for use in pneumonia. Telavancin, dalbavancin, and oritavancin are lipoglycopeptides that maintain activity against MRSA, vancomycin-intermediate *S. aureus*, and heterogeneous vancomycin-intermediate *S. aureus* strains. Telavancin may be used for the treatment of nosocomial pneumonia when alternatives are not available, but patients with preexisting renal impairment have had higher mortality with this agent. Telavancin should not be used in pregnancy and also may prolong the QTc interval. Use outside of soft tissue infections is currently being investigated for dalbavancin and oritavancin.

**Infections Caused by Coagulase-Negative Staphylococcus Species**

There are more than 40 species and subspecies of CoNS, and they are the most common microbes inhabiting the skin. CoNS are a frequent cause of “contaminated” blood cultures but have evolved as major nosocomial pathogens. With changes in healthcare and increases in immunosuppressed populations, the role of CoNS as pathogens is established in some cases and evolving in others. More than 70% of isolates in a healthcare setting are oxacillin resistant. The ability of CoNS to adhere and form biofilm on the surface of invasive devices is their major virulent feature. They account for 30% of healthcare-associated bloodstream infections (usually from intravascular catheters) and are 1 of the 3 most common pathogens causing this condition. CoNS bacteremia should be considered clinically significant when more than 1 blood culture yields the same organism; when time to culture positivity is less than 24 hours; and when signs of sepsis are present, particularly in immunocompromised patients and those with implanted medical devices. CoNS account for 15% to 40% of cases of prosthetic valve endocarditis (they rarely cause native valve endocarditis, except *Staphylococcus lugdunensis*). CoNS cause 50% to 60% of CIED infections (they are the most common cause of LVAD infections (together with *S. aureus*) and one of the most common causes of sepsis during ECMO. CoNS can cause 20% to 30% of vascular graft infections and account for 30% to 40% of orthopedic prosthetic device infections. Other important syndromes include infections of CSF shunts, infections of peritoneal dialysis catheters, peritonitis due to VP shunt and peritoneal catheter infections, surgical site infections, endophthalmitis, and infections of genitourinary prostheses. CoNS are an important cause of bloodstream infections in patients who receive
solid organ and hematopoietic stem cell transplant, burn patients, and neutropenic hosts. *S. epidermidis* and *Staphylococcus haemolyticus* are the most common CoNS involved in many of the conditions described. *S. lugdunensis* is an exceptionally virulent species that behaves (and should be treated) like *S. aureus*, and its presence in blood cultures should not be regarded as a contaminant; about 90% of isolates were found to be clinically significant in one review. Only 25% of *S. lugdunensis* strains produce β-lactamases, and methicillin resistance is not common. Management is individualized to the condition and the host; frequently, removal of involved hardware is required along with appropriate antimicrobial therapy.

REFERENCES


